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Annotations

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Is neonatal cerebral ultrasound just for the voyeur?

Few neonatal intensive care units consider themselves well equipped unless high quality 'real-time' ultrasound facilities are available round the clock. Looking inside an infant's head is an interesting occupation and as a research tool has considerably advanced our understanding of lesions due to vascular compromise, but what is its clinical role? Should Doppler ultrasound be introduced for clinical purposes, and what is the value of information obtained by these methods? The answer to these questions today may be considered by some to be self evident, but in the post-Griffith era an attempt to justify the cost of this relatively expensive piece of equipment is perhaps of some value.

What are we seeing?

Real time ultrasound was first used in a neonatal intensive care unit to detect intraventricular haemorrhage in 1978¹; and gradually the number of conditions diagnosed by this technique has increased.² In recent years, and with the use of higher frequency transducers, periventricular leucomalacia has been recognised as a particularly important abnormality in premature infants. In addition, frequent scanning permits the early detection of increasing ventricular size or extension of haemorrhagic lesions.

Real time ultrasound of the infant's brain has been widely adopted because the manufacturers of ultrasound equipment have developed machines that produce, by means of sound, an image which appears to resemble the structure of the brain. We interpret echoes by reference to anatomical slices produced by pathologists and believe that the image gives us the same information, but this may be misleading. We now know that extensive echodensity within the brain may be associated with a macroscopically normal brain at necropsy³ and, conversely, pathological features within or around the brain may not be detected by ultrasound. There is a need for accepted definitions on which to base diagnoses, but to date there are few such agreed descriptions of pathological appearances.

The problem of diagnostic criteria exists for all imaging techniques; indeed, real time ultrasound is better evaluated in this respect than computed tomography, as scanning normal babies by ultra-

sound is more acceptable. The value of any imaging technique may be judged by measurement of its positive and negative predictive value, and its use in detecting abnormalities may be assessed by its sensitivity and specificity for each particular lesion. Several studies are now available that report the accuracy of ultrasound in the diagnosis of periventricular haemorrhage, but correlation of appearances with other conditions is unfortunately limited.

What does it mean?

Ultrasound was rapidly accepted into the neonatal unit because it showed abnormalities not easily detectable by any other means. Germinal matrix haemorrhage and intraventricular clot produce striking appearances, and these lesions were initially thought to be associated with the adverse outcome of some infants. Research often lagged behind clinical use and much anxiety was generated among neonatal unit staff and the infant's parents when these lesions were diagnosed. It was only some years later when it was realised that uncomplicated haemorrhage confined to the ventricles was a benign condition.^{4 5}

The potential clinical value of real time ultrasound can be divided into two separate categories: intervention and prognosis. Ventricular dilatation occurs in a large proportion of premature infants after intracranial haemorrhage, and some go on to develop hydrocephalus. It is in this group that intervention may be important. Regular ultrasound assessment will give the first indication of enlargement of the ventricles, but to date no clear guidelines exist as to when to intervene in the management of these infants. The outcome in such infants may be modified by the early detection and management of posthaemorrhagic hydrocephalus, and research is continuing. At present there is little evidence that knowledge of progressive ventricular enlargement aids the clinician, and the clinical role of ultrasound in this context is still uncertain.

Reliable prognostic information based on ultrasound scans is just becoming available but there is still considerable confusion in this area. There is now evidence that cavitating periventricular leucomalacia is a sinister lesion in terms of prognosis and

further variables such as the size, extent, and position of the cavities are important in more accurately predicting both cerebral palsy and developmental delay.^{5,6} Babies can survive massive haemorrhage with fairly minor neurological deficit,⁷ and there are no studies reporting the outcome of a large group of unselected babies prospectively scanned with ultrasound and found to have cystic periventricular leucomalacia. The most worrying occurrence is the withdrawal of intensive care because of ultrasound findings alone, a practice which I believe is common (at least in the United Kingdom) in many neonatal units that have ultrasound facilities, but no consensus as to the criteria for termination of assisted ventilation. Thus ultrasound scanning for either diagnostic or prognostic reasons is a somewhat tenuous justification for its routine use. It is, however, true that consistently normal scans are associated with a low risk of adverse neurodevelopmental outcome and as such are reassuring to parents and nursery staff.^{4,5}

Who should scan the infants?

Radiologists and neonatologists most commonly undertake ultrasound brain scanning in the neonatal unit and this largely depends on who owns the machine. In my view the person with the most experience and interest is the one who is most appropriate, but unfortunately it may be a fairly junior doctor (or perhaps radiographer) who performs the routine scans.

The clinical value of ultrasound scans has been discussed above, and major therapeutic or management decisions may be based on interpretations performed by these personnel. It is alarming that no recognised course, diploma, or formal period of training is necessary before anyone can pick up an ultrasound transducer. The distinction between experience and inexperience is blurred; this happens in few other fields of medicine with quite the same implications.

What use is Doppler?

Doppler ultrasound has been used to detect flow in the anterior cerebral artery in neonates since 1979,⁸ and there are now many reports of its use. Fairly inexpensive equipment, together with ease of obtaining signals, has made this technique attractive to a number of observers.⁹ It is, however, unfortunate that many studies have been performed without appropriate methodological care and with poor instruments. The practical value of Doppler ultrasound is still not clear. We have recently reported its value in predicting outcome after intrapartum

asphyxia, but before this technique becomes clinically useful further prospective studies will be necessary.¹⁰

Conclusion

Ultrasonography has made a major contribution to neonatal neurology and increased understanding of the variety of cerebral lesions which affect the perinatal brain; it is easy to believe that this valuable research tool also has a clear role in clinical neonatology. Ultrasonography has become a ubiquitous technique for investigating the neonatal brain for all the reasons discussed above, but it is difficult to assemble a convincing argument in favour of buying high resolution equipment solely for brain scanning. The role of real time ultrasound can be better justified for the diagnosis of neonatal cardiac or renal abnormalities than for cerebral lesions, because there the therapeutic implications for a large variety of abnormalities are much more clear cut. It is considerably easier to justify a multipurpose machine dedicated for use in a neonatal unit, thereby fulfilling the dual aims of clinical utility as well as more esoteric voyeurism.

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Child psychiatry and the undergraduate

A recent survey of undergraduate teaching in child and adolescent psychiatry raised several points, among them the question of what paediatricians might expect from undergraduate training in this branch of children's medicine.¹ It is generally accepted that the overall prevalence of childhood psychiatric disorder lies between 7% to 14% with the higher rates obtaining in areas of greater social disadvantage.² Children with such disadvantaged backgrounds are common in paediatric clinics so it is perhaps not surprising that Fitzgerald found that 44% of 7-11 year olds attending paediatric surgical outpatients and 25% attending paediatric medical outpatients showed 'considerable behavioural deviance'.³ Garralda and Bailey identified 23% of 7-12 year olds attending general practice as having psychiatric disorders.⁴ In a subsample of this group psychiatric disorder seemed a relevant factor contributing to somatic consultations.

These figures suggest that it would be reasonable for paediatric trainees to expect a thorough grounding in child and adolescent psychiatry to deal with their immediate paediatric workload or to equip them for a future general practice workload, and in fact some senior house officers in paediatrics are undertaking vocational training for general practice. Postgraduate experience in child and adolescent psychiatry is recognised as being an important component in training in adult psychiatry,⁵ but it is difficult for trainees in paediatrics to obtain such training as virtually all senior house officer and registrar posts in child and adolescent psychiatry are now integrated into rotational training schemes in psychiatry. Adequate undergraduate training is thus essential.

On average, only 20 hours of teaching time is available for teaching of child and adolescent psychiatry.¹ Of 28 medical schools surveyed 10 had very little or no teaching of child and adolescent psychiatry when the students were with the paediatric firm. None of these schools had teaching aims for child and adolescent psychiatry that would be relevant to paediatrics. Of the other 18 schools (where some child and adolescent psychiatry was taught within paediatrics) only six made any reference to joint teaching with paediatricians and only eight cited teaching aims relevant to paediatrics—for example, understanding the impact of illness on a child, provision of treatment skills for future paediatricians, and breaking bad news to parents. It

seems unlikely that undergraduates will receive paediatrically orientated psychiatry teaching unless this occurs within the paediatric firm and even then not all schools will provide such teaching. Is this something to be concerned about? What aspects of such teaching would be relevant to future paediatricians? We suggest the following:

- (i) Specific training in how to interview children and whole families.
- (ii) Recognition and diagnosis of specific childhood psychiatric disorders.
- (iii) Recognition of specific aetiological factors that may be influencing the presentation, course, or compliance with treatment of paediatric disease such as childhood psychiatric disorder; family influences (marital discord, inconsistent discipline); social influences (school and neighbourhood); individual characteristics of the child (temperament, intelligence, social and emotional development); psychiatric disorder in parents.
- (iv) Understanding of the interplay between psychosocial factors and physical factors in paediatric disease.
- (v) Knowledge of the pattern of services available for children with psychiatric disorder.
- (vi) Provision of management skills for dealing with common behaviour problems (tantrums, eating and sleeping problems, elimination problems) either directly or indirectly via treatment recommendations to referring general practitioners.

There are other advantages accruing from a close relation between the teaching of paediatrics and child and adolescent psychiatry. Joint teaching exposes each specialty to the other and encourages good liaison if clinical as well as theoretical teaching is carried out together. In this way such undergraduate teaching can become a component of the postgraduate training of paediatricians in child psychiatry as well as the postgraduate training of child psychiatrists in paediatrics. At Queen Mary's Hospital for Children, Carshalton, where St George's students are routinely taught in this way, there are frequent comments in the students' feedback about the value of seeing such a close

working/teaching relation. There is a dearth of research evidence concerning the psychological problems that actually present to routine paediatric clinics and wards—a closer relationship between the two specialties would help rectify this lack of knowledge.

In summary, childhood psychiatric disorder is common but the teaching of child and adolescent psychiatry is patchy and its relevance to paediatrics not always recognised in the design of teaching programmes. Its value is more likely to be recognised where it is taught within the paediatric firm. Close liaison between paediatricians and child and adolescent psychiatrists about teaching aims, curriculum planning, and time allocation would be of benefit to both specialties. Child and adolescent psychiatry is a rather fragile specialty, which traditionally has had much of its clinical base placed away from acute medicine in the community. It needs the support and involvement of paediatricians if it is to deliver the training that paediatricians would expect for their junior staff.

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Original articles

Long term follow up of patients with early onset anorexia nervosa

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SUMMARY A long term follow up (mean 7.2 years) of 30 children with anorexia nervosa (mean age at onset 11.7 years) was carried out. The outcome was good in only 18 (60%), 10 children remaining moderately to severely impaired and two died. Poor prognostic factors included early age at onset (<11 years), depression during the illness, disturbed family life and one parent families, and those in which one or both parents had been married before.

We have previously described 48 children up to 14 years of age who met the diagnostic criteria of anorexia nervosa.¹ The group (which included 15 boys) had a mean age at onset of 11.7 years (range 7.7 to 13.2). Half the children were prepubertal at the time of referral. The most common clinical features after refusal of food, which was present in all the children, were physical wasting in 40 (83%), depression in 27 (56%), fear of fat in 24 (56%), distorted body image — that is perceiving self as fat although physically wasted—in half, and self induced vomiting in 19 (40%). Other features occurring less often included excessive exercising, obsessions or compulsions, binge eating and laxative abuse. The most common reasons for refusing to eat were the fear of becoming fat and various physical symptoms such as abdominal pain, nausea, or a feeling of fullness. Disturbed family life was common, and over half the families had several adverse characteristics. The correct diagnosis had often been missed or delayed.

This study aimed to investigate the long term outcome of early onset anorexia nervosa and identify prognostic indicators.

Patients and methods

We tried to follow up all the children who had been described in the earlier study and whose treatment had been completed more than two years before ($n=44$), as information obtained from a follow up of less than two years is not considered to be adequate in patients with anorexia nervosa.² Information is

required on weight and growth, menstrual state, eating behaviour, mental state, and psychosocial and psychosexual adjustment³; we obtained it in four ways.

INTERVIEW WITH PATIENT

After a physical examination a semistructured interview adapted for this younger age group was completed by a visiting consultant who was experienced and not managing the patients and their treatment.²

POSTAL QUESTIONNAIRE

Six patients were reluctant to be interviewed but agreed to complete a postal questionnaire based on the interview. This information was supplemented by medical reports.

GENERAL PRACTITIONER'S QUESTIONNAIRE

A short questionnaire devised for this study was circulated to each patient's general practitioner. Information requested included current weight and height, and details of menstrual functioning and general state of health.

OTHER QUESTIONNAIRES

Corroborative data were obtained using firstly, three self report questionnaires:—the general health questionnaire⁴; the eating attitudes test⁵; and the Great Ormond Street depression scale A: (unpublished). Secondly, parents or 'significant others' were asked to complete questionnaires: the Great Ormond Street depression scale B: (unpublished),

and the Rutter scale A.⁶ Thirdly, for children under the age of 16 at the time of follow up the school teacher was asked to complete a questionnaire.⁷

When sufficient information obtained from the interview and the questionnaires became available it was used to rate outcome on five different scales and three scores.² These measures, designed to assess outcome as comprehensively as possible, and widely accepted in research into anorexia nervosa, are given below.

Nutritional state (scale A) included ratings of current food intake, worries about body size, and measurements of body weight and height.^{8,9}

Menstrual function (scale B) recorded whether menstruation was absent, occasional and irregular, intermittently cyclical, or regularly cyclical, using a four point scale.

Mental state (scale C) rated the degree of psychiatric disturbance at the time of follow up using a four point scale.

Psychosexual state (scale D) rated the subject's attitude towards sexual matters, the aims in sexual relationships, the amount of active sexual behaviour, and attitude towards menstruation.

Psychosocial adjustment (scale E) rated the quality of relationships with other members of the family, the amount of independence from the family appropriate for the subject's age, social contacts outside the home, and occupational record or school attendance.

We used three outcome scores: the average outcome score was calculated using the scores of all five scales (A to E), the physical outcome score was calculated using scores based on menstrual state (scale B) and weight, and the specific outcome score was calculated using scores obtained from scales A and B.

Ordinal data were generated from outcome scores and several correlations were analysed in an attempt to identify specific prognostic indicators. Because of the small sample size, the Statistical Package for the Social Sciences was used to calculate Kendall's rank correlation coefficient (τ).

Results

We obtained adequate information about 23 female and seven male subjects. The mean (range) follow up was 7.2 (2-17) years and mean age was 20.8 (14-30) years. Of the original sample of 48 children, six subjects could not be traced, four refused to participate, in four insufficient information was available, and it was too early to follow up four children. Two had died; the first was a boy aged 14 who had an apparently unrelated acute asthmatic attack, and the second was a girl of 12, who had

prolonged and persistent vomiting which ultimately led to rupture of the oesophagus. Despite surgical repair it ruptured again and she bled to death.

Weight is the most commonly used measure of outcome, but a more useful measurement is that given by the Tanner-Whitehouse standards^{8,9} in which weight for height, adjusted for age, is expressed as a percentage, 100% being normal and less than 80% indicating wasting. In the original sample 42 children (87%) scored less than 80% and at follow up only three subjects (11%) were wasted (table 1). The remaining 25 scored between 82% and 122%, mean 92%. Six patients scored over 100% weight for height.

SCALES AND OUTCOME SCORES

The results are summarised in tables 2 and 3. The totals for each score of scale and outcome differ because information was sometimes not available for one or more of the scales. The two children who died are included in the 'poor outcome' group. On each measure of scale and outcome a good score was obtained by between half and three quarters of the sample. We believe that the four subjects who refused to participate all had a poor outcome, and

Table 1a *Weight for height adjusted for age (expressed as %) at time of first refusal*

Weight/height (%)	No of patients	% Of total series
40-59	1	2
50-59	0	0
60-69	19	40
70-79	17	35
80-89	9	19
90-99	2	4
Total	44	100

Table 1b *Weight for height adjusted for age (expressed as %) at time of follow up*

Weight/height (%)	No of patients	% Of series followed up
60-69	1	3
70-79	1	3
80-89	5	17
90-99	10	33
100-109	5	17
110-119	0	0
120-129	1	3
Information not available	5	17
Died	2	7
Total	30	100

Table 2 *Grading within scales at follow up*

Scale	Good No (%)	Intermediate No (%)	Poor No (%)	Total No
Eating difficulties (A)	17 (65)	5 (19)	4 (16)	26
Menstruation (B)	12 (55)	3 (14)	7 (31)	22
Mental state (C)	13 (62)	4 (19)	4 (19)	21
Psychosexual adjustment (D)	10 (50)	7 (35)	3 (15)	20
Psychosocial adjustment (E)	16 (59)	6 (22)	5 (19)	27

Table 3 *Grading of scores of outcome*

Score	Good No (%)	Intermediate No (%)	Poor No (%)	Total No
Physical outcome (scale B + weight)	18 (67)	2 (7)	7 (26)	27
Specific outcome score (scales A and B)	19 (70)	1 (4)	7 (26)	27
Average outcome score (all scales, A-E)	15 (55)	3 (11)	2 (7)	20

we have included these in adjusted outcome scores (table 4) which we consider more accurately reflects the prognosis—that is, a good outcome in only about 60% of the sample.

When they were asked to rate their own progress in general terms, 19 subjects (66%) claimed to have recovered, six (21%) thought they had improved, one thought she had remained the same, and one claimed to be worse. At the time of follow up, eight subjects (27%), seven girls and one boy, had required further inpatient treatment since their discharge from hospital. Of the 22 subjects who were aged 18 or more at follow up, only two were married, both women with children; for one it was her second marriage. None of the others had been married, although at least four were cohabiting.

Table 4 *Adjusted scores of outcome*

Score	Good No (%)	Intermediate No (%)	Poor No (%)	Total No
Physical outcome score (scale B + weight)	18 (58)	2 (6)	11 (36)	31
Specific outcome score (scale A + B)	19 (61)	1 (3)	11 (36)	31
Average outcome score (all scales A-E)	15 (62)	3 (13)	6 (25)	24

PROGNOSTIC INDICATORS

The data indicated that certain variables were associated with a poor outcome.

Age at referral

Young age at referral had a poor prognosis according to three different measures of outcome: low weight at follow up ($p < 0.001$, τ 0.43), low specific outcome score ($p < 0.05$, τ 0.35), and low physical outcome score ($p < 0.05$, τ 0.39). Furthermore, young age at the onset of eating difficulties was also positively correlated with low weight at follow up ($p < 0.05$, τ 0.35).

Hospital admission

The longer the hospital admission, the more likely it was that there would be a low specific outcome score ($p < 0.01$, τ 0.41); a low average outcome score ($p < 0.05$, τ 0.35); a high score on the Great Ormond Street depression scale—self rated ($p < 0.01$, τ 0.33); and a high score on the Great Ormond Street depression scale rated by 'significant others' ($p < 0.005$, τ 0.44).

More than one hospital admission had a poor prognosis in terms of low weight at follow up ($p < 0.05$, τ -0.31) and both forms of the Great Ormond Street depression scale ($p < 0.05$, τ 0.25 and 0.31).

Depressive features

Depressive features during the initial illness had a poor prognosis according to three measures of outcome: high scores on both forms of the Great Ormond Street depression scale ($p < 0.01$, τ 0.26+0.27), low physical outcome score ($p < 0.05$, τ 0.37), and low average outcome score ($p < 0.05$, τ 0.38).

Family structure

Children from one parent families, families in which one or both parents had been married before, and families in which several generations lived together had a poor prognosis according to four measures of outcome: low physical outcome ($p < 0.01$, τ 0.35), low specific outcome score ($p < 0.01$, τ 0.35), low score on scale C ($p < 0.05$, τ 0.44), and low score on scale D ($p < 0.05$, τ 0.36).

Other variables

None of the following factors seemed to be of any prognostic importance: social class, gender, weight at referral, length of illness at referral, history of excessive exercising, distorted body image, or fear of fatness.

CLINICAL FINDINGS

During the follow up interviews several important

issues were identified by patients. These, many of which overlap, form an essential part of the total picture of anorexia nervosa and illustrate a subjective view of the disorder.

Battles

Many spoke of the battles they had had, particularly with their parents, and often with their mothers with whom they felt they had a close bond. Later these battles were transferred to the hospital indicating that inner conflicts were first expressed within the family and then included difficult relationships with hospital staff.

Control

Control was considered to be important by several subjects. Many felt that they had been forced to accept admission to hospital despite their protests. Some felt that they had accepted that matters had got out of control, yet others remembered struggling for what they felt to be their freedom. This freedom was equated with their own emotional survival. Many had an overwhelming sense of being controlled, which in some cases was replaced by a more positive attitude: "I realized that I could do things for myself and I had control, and I could also see that others didn't have this control" . . . "I felt good about myself, that I could control myself, whereas before, I felt I had no control and was very frightened".

Growing up

Some subjects said that they had been frightened of growing up as this meant insecurity. Some also mentioned that they got much more attention from their parents when they acted as if they were younger, and many stated that they noticed how much more attention they got than their brothers and sisters.

Overinvolvement

Some identified feelings of being "tied", or "stuck", or "unable to move", in their relationships with their mother. One mother who was interviewed said "I wanted to be at one with my daughter" and spoke of the distress to both when this could not be achieved. Many recalled that they had desperately wanted to get home to their families. Some considered this to be the major influence in regaining weight—for example, "I had to get out, as I became so depressed being away from my family, and this pushed me to gain weight and get home".

Dependence and independence

Many spoke about their attempts to achieve autonomy and independence. The final insult was often

the admission to hospital against the subject's will. Some recognised their dependence and the conflicts that arose from this; on the one hand, they were tied to their parents and wanted this, but on the other hand they wanted independence and freedom. One person said: "I was tied to my parents and felt very dependent on them—I even broke off my engagement".

School difficulties

A few patients felt that their relationship with their parents had not been difficult, but that they had experienced considerable difficulties with their peer group particularly at school. Some felt isolated and others said they suffered from rivalry among their friends. This made them feel sensitive and vulnerable to attacks from others.

Loneliness

Almost all said that they had felt alone and isolated, both before and during the illness. They felt that no one really understood what they were experiencing. They lost their self respect, decisions were made for them, and they were not accepted as independent people. They often felt a sense of worthlessness, which led to depression and anxiety.

Discussion

Anorexia nervosa is a difficult illness about which to obtain accurate information over a long period. Many patients do not wish to be reminded of their earlier problems; others cannot be traced. Follow up studies are only adequate if well defined diagnostic criteria are used in well defined samples. The follow up should not be less than two years, and the sample must be as complete as possible. Parents should be interviewed, and corroborating information obtained from close relatives, the general practitioner, or other doctors. The complexity of the illness necessitates evaluation of a number of factors, body weight alone being insufficient. These should include nutrition, menstruation, eating behaviour, mental state, and psychosocial and psychosexual adjustment.

A number of adequately controlled studies of anorexia nervosa of later onset (age 15 or more) have been carried out,¹⁰ but there are few studies in younger children.³ In general, with both types of the illness the outcome is unsatisfactory. Persisting psychiatric problems are common (in 50–70%) especially depression, obsessional behaviour, and social phobia. Psychosis is, however, rare. Psychosocial adjustment is variable, but psychosexual adjustment is often poor. Eating difficulties persist in over half the patients, but nutritional and men-

strual condition improves in between half and two thirds of patients. The mortality among adult patients averages 7%, and in childhood studies 3%.

Our results are comparable with those of earlier childhood onset studies and are of additional importance because of the long mean period of follow up, and the relatively large sample. The children were all seriously ill at the time of referral and several, though they undoubtedly had anorexia nervosa, were much younger than is usually expected in this illness.

A number of worries arise as a result of this study. As previously mentioned¹ the diagnosis is often missed; because early age of onset has a poor prognosis, it is important to recognise such children quickly and treat them effectively. Menstruation remained impaired in nearly half the girls, raising doubts about their ability to have children.

The unsatisfactory prognosis indicates the need for more effective treatment. The clinical information gained at follow up is very helpful in highlighting a number of issues that patients were unable to discuss during their illnesses. Both psychological and social problems are commonplace, and point to the need for treatment of both the individual child and the family.

In conclusion, the long term outcome for patients with early onset anorexia nervosa is unsatisfactory; between a third and a half of a sample of 30 children remaining impaired in at least one (and usually in several) aspects of physical and psychological function. Over a quarter had required further admission to hospital with psychiatric disorders. Issues of control, growing up, independence v dependence, overinvolvement with parents, and loneliness were common problems for these children. The severity and complexity of the illness demands early, skilled, and comprehensive treatment, full details of which have been published elsewhere.¹¹

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Surfactant treatment and incidence of intraventricular haemorrhage in severe respiratory distress syndrome

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SUMMARY As part of a multicentre study of porcine surfactant administration in respiratory distress syndrome, 29 babies weighing 2000 g or less were studied in the neonatal intensive care unit of the Royal Maternity Hospital, Belfast. Fourteen babies of a mean gestational age of 28.1 weeks were randomly allocated to the treatment group (200 mg/kg phospholipid given intratracheally) and 15 babies of a mean gestational age of 28.7 weeks formed the control group. All babies had severe respiratory distress syndrome (oxygen requirement over 60%, mechanical ventilation and age 15 hours or less). Almost immediate improvement in oxygenation was seen in the treated group so that oxygen concentrations could be reduced and remained significantly lower than those of control babies for the first seven days of life. Alveolar-arterial oxygen gradients were also significantly different for the first five days after treatment. More babies in the treatment group survived (79% v 40%) but the difference was not significant. The incidence of pneumothorax and of intraventricular haemorrhage, however, was significantly lower in treated babies compared with controls. For babies weighing less than 1200 g the risk of developing or extending intraventricular haemorrhage after entry to the study was also reduced in the treatment group (29% v 100%).

Surfactant replacement has been shown to be an effective treatment for neonatal respiratory distress syndrome in a number of non-randomised¹⁻³ and randomised controlled trials.⁴⁻¹¹ The latter trials were designed to prevent respiratory distress syndrome^{5,9} or to treat established disease (intervention studies).^{4,10,11} Three studies showed reduced mortality in treated babies,^{5,8,9} and one showed a decreased incidence of intraventricular haemorrhage after prophylaxis with surfactant at birth.⁵

We report the results of a randomised intervention study of surfactant replacement in neonatal respiratory distress syndrome, which for the first time shows a decreased incidence of intraventricular haemorrhage in treated babies.

Surfactant

The surfactant was prepared from minced porcine lungs by chloroform-methanol extraction and liquid gel chromatography,¹² and it contains roughly 99%

of polar lipids, mainly phospholipids, and 1% of hydrophobic proteins (molecular weight <15 000). After chromatography the material was dissolved in chloroform and passed through a 0.2 µm filter. The subsequent steps of the preparation procedure, including evaporation of the chloroform and suspension in saline, were carried out under sterile conditions. Repeated bacterial cultures from the original batch and from the individual phials after the intubation procedure gave negative results. The physiological activity of our surfactant has been documented in experiments on preterm newborn rabbits receiving artificial ventilation.^{12,13}

Patients and methods

Twenty nine preterm infants with birth weights of 700-2000 g were entered in the study. All infants had clinical and radiological findings of severe respiratory distress syndrome¹⁴ between two and 15 hours from birth and required mechanical ventilation with oxygen concentrations of 60% or more.

These babies were all severely ill and had a median age at the start of mechanical ventilation of less than 30 minutes. Only 10% of babies having mechanical ventilation for respiratory distress syndrome were ill enough to fulfil the study entry criteria. Babies were excluded if they had severe birth asphyxia (Apgar score of <5 at five minutes), streptococcal pneumonia, major congenital anomalies, or intraventricular haemorrhage (grade III-IV on ultrasound scan¹⁵) before entry into the study. Informed consent was obtained from the parents of each baby and the study protocol was approved by the research ethical committee of the Queen's University of Belfast.

After enrolment babies were randomly allocated into control and treatment groups by a consultant neonatologist. Randomisation was stratified by birth weight of <1200 g and ≥1200 g, to ensure equal numbers of smaller babies in each group. Treated babies were disconnected from the ventilator and 1.25 ml/kg (phospholipid concentration 80 mg/ml) of surfactant was instilled into each main bronchus via a 5 French gauge feeding tube. Between and after instillations the baby was ventilated by manual bagging for one minute. In control babies manual ventilation for two minutes was performed but no surfactant was instilled. The babies were then reconnected to the ventilator at the same oxygen concentration and ventilator settings. Clinical care of the babies after enrolment was by consultants and junior doctors who were unaware of the randomisation procedure. Babies in both groups were assessed by serial chest radiographs, arterial blood gases, ventilator settings, echocardiography, and calculated

alveolar-arterial oxygen gradients (A-aDO₂) using a modified equation, where FiO₂ is the fraction of inspired oxygen concentration⁵.

$$A-aDO_2 = FiO_2 \times 713 - \frac{PaCO_2}{0.8} - PaO_2$$

Complications such as pneumothorax¹⁶ and bronchopulmonary dysplasia¹⁷ were diagnosed radiologically, patent ductus arteriosus by echocardiography,¹⁸ and intraventricular haemorrhage by ultrasound scan.¹⁵⁻¹⁹ Echocardiography and cerebral ultrasound scans were performed before entry and thereafter at intervals of 15 minutes, one, four, six, and 24 hours, and daily until 10 days. Babies were studied until death or discharge from hospital. Outpatient follow up of survivors at intervals of three months continued but is not the subject of this report.

Statistical assessment was by Fisher's exact test, independent *t* test, and Mann-Whitney U test where appropriate. All *p* values quoted are two tailed.

Results

The clinical characteristics of the two groups of babies are shown in table 1. There were no significant differences between the groups for any of these variables. After surfactant instillation there was an immediate reduction in oxygen requirement (FiO₂) (fig 1). This was seen at 15 minutes (not shown) and remained lower in treated babies for up to seven days. Similarly, A-aDO₂ was significantly lower in treated babies up to five days of age (fig 2). Not all babies showed sustained response so that the standard deviations were quite large for both FiO₂

Table 1 Clinical characteristics of treated and control groups

	Treated group (n=14)	Control group (n=15)	<i>p</i> Value
Birth weight (g) (mean SD)	1316 (303)	1329 (347)	0.91
Gestation (weeks) (mean SD)	28.1 (1.4)	28.7 (2.2)	0.46
Weight <1200 g (No %)	7 (50)	5 (33)	0.59
Males (No %)	8 (57)	10 (67)	0.88
Inborn (No %)	11 (79)	10 (67)	0.77
Given antenatal steroids (No %)	1 (7)	1 (7)	1.0
Antepartum haemorrhage (No %)	8 (57)	4 (27)	0.20
Pre-eclampsia (No %)	2 (14)	3 (20)	1.0
Prolonged rupture of membranes (No %)	5 (36)	3 (20)	0.60
Twin pregnancy (No %)	1 (7)	1 (7)	1.0
Caesarean section (No %)	11 (79)	6 (40)	0.08
Breech delivery (No %)	—	4 (27)	0.11
Apgar scores (median range)			
1 minute	3 (2-5)	3 (2-7)	0.70
5 minutes	7 (5-9)	7 (5-9)	0.47
Intubated at birth (No %)	10 (71)	10 (67)	1.0
Age at entry (hours) (median range)	5 (2-13)	7 (2-15)	0.16
FiO ₂ at entry (mean SD)	0.79 (0.12)	0.76 (0.10)	0.42

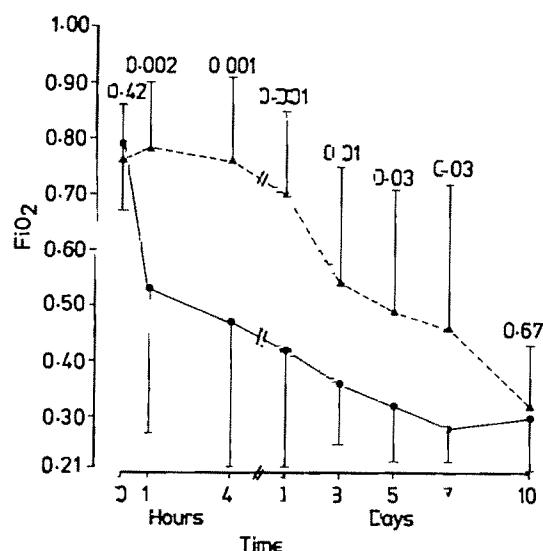


Fig. 1 Comparison of oxygen requirement (FiO_2) in treated $\bullet$ — $\bullet$ and control $\triangle$ — $\triangle$ groups before entry into the study (time=0) and at one hour, four hours, and one, three, five, seven, and 10 days afterwards. Mean (SD) are shown with p values derived from two tailed independent t tests.

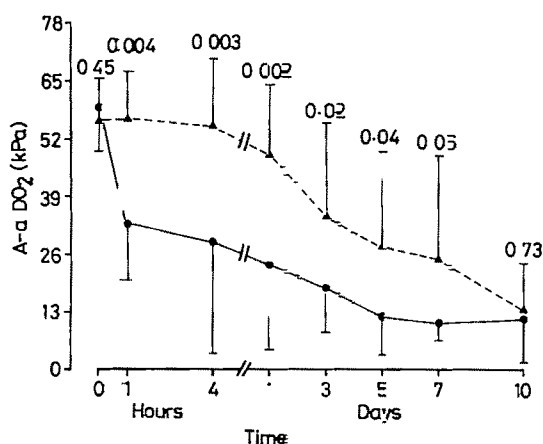


Fig. 2 Comparison of alveolar-arterial oxygen gradients ($A-aDO_2$) between treated $\bullet$ — $\bullet$ and control $\triangle$ — $\triangle$ groups.

and $A-aDC_2$. To evaluate the significance of differences where the data are not parametrically distributed we also used Mann-Whitney U tests. The p values quoted in the figures are for independent t tests but we found no changes after Mann-Whitney U tests except for $A-aDO_2$ at five days when the difference between the groups was not significant ($p=0.07$). Table 2 shows the changes in ventilator

Table 2 Mean (SD) ventilator settings at randomisation and at four hours, 24 hours, and three days after entry into study

	Treated group (n=14)	Control group (n=15)	p Value
Peak pressure (cm H_2O)			
At randomisation	25 (5)	22 (4)	0.09
After entry			
4 hours	21 (7)	24 (6)	0.29
24 hours	19 (4)	26 (7)	0.005
Three days	15 (9)	26 (8)	0.004
Mean airway pressure (cm H_2O)			
At randomisation	9 (2)	9 (2)	0.97
After entry			
4 hours	7 (4)	10 (4)	0.12
24 hours	5 (3)	10 (4)	0.001
Three days	4 (3)	10 (4)	0.001
Rate (breaths/minute)			
At randomisation	47 (9)	44 (9)	0.38
After entry			
4 hours	44 (13)	46 (10)	0.60
24 hours	32 (12)	51 (13)	0.001
Three days	24 (18)	43 (12)	0.005
Inspiratory expiratory ratio			
At randomisation	0.8 (0.2)	0.9 (0.3)	0.38
After entry			
4 hours	0.8 (0.4)	1.0 (0.4)	0.40
24 hours	0.6 (0.4)	1.2 (0.9)	0.03
Three days	0.4 (0.3)	0.9 (0.4)	0.001

settings from randomisation up to three days after entry into the study. Oxygen concentrations fell immediately after administration of surfactant; ventilator settings were reduced after a delay of about 24 hours. Peak airway pressure, mean airway pressure, ventilator rate, and inspiratory:expiratory time ratio were all significantly lower in treated infants after 24 hours.

Table 3 compares the outcome for the two groups. Although survival was greater for treated babies, this did not attain significance using a two tailed Fisher's exact test. For one tailed testing, the mortality was lower for treated babies at the 5% level. Pneumothorax ($p=0.005$) and bilateral pneumothoraces ($p=0.019$) occurred more commonly in control babies. Intraventricular haemorrhage was also seen more often in control infants (87% v 29%, $p=0.004$). Five babies had grade I or II intraventricular haemorrhage at entry into the study, three of whom were in the treated group (table 4). Development of new intraventricular haemorrhage or extension occurred significantly more commonly in control babies ($p=0.0003$), and this was also true for babies weighing <1200 g ($p=0.05$). (One treated baby had grade II intraventricular haemorrhage that progressed to grade III; one control baby progressed from grade I to

Table 3 Comparison of outcomes in treated and control groups

	Treated group (n=14)	Control group (n=15)	p Value
Survived (No %)	11 (79)	6 (40)	0.08
Survived weighing <1200 g (No %)	5/7 (71)	0/5 —	0.053
Pneumothorax (No %)	3 (21)	12 (80)	0.005
Bilateral	1 (7)	8 (53)	0.019
Muscle relaxants given before pneumothorax (No %)	9 (64)	12 (80)	0.60
Intraventricular haemorrhage (No %)	4 (29)	13 (87)	0.004
Patent ductus arteriosus (No %)	8 (57)	6 (40)	0.58
Indomethacin given (No %)	8 (57)	4 (27)	0.20
Pulmonary interstitial infiltrates on chest radiograph (No %)	9 (64)	3 (20)	0.039
Bronchopulmonary dysplasia in survivors (No %)	3/11 (27)	2/6 (33)	1.0
Duration of IPPV* in survivors (hours) (median range)	194 (47–1510)	239 (141–1472)	0.65
Duration of oxygen treatment in survivors (hours) (median range)	776 (190–3657)	661 (400–2027)	0.74
Age at death (days) (median range)	1 (1–19)	4 (1–29)	0.60

*IPPV=intermittent positive pressure ventilation

Table 4 Occurrence of intraventricular haemorrhage and its grade in both groups†

	Treated group		Control group	
	All babies (n=14) (no (%))	Weight <1200 g (n=7) (no (%))	All babies (n=15) (no (%))	Weight <1200 g (n=5) (no (%))
Intraventricular haemorrhage before entry	3 (21)	2 (28)	2 (13)	1 (20)
Grade I	0	0	1	0
Grade II	3	2	1	1
Intraventricular haemorrhage at death or discharge	4 (29)	3 (43)	13 (87)**	5 (100)
Grade I	0	0	2	1
Grade II	2	1	6	2
Grade III	1	1	2	0
Grade IV	1	1	3	2
Intraventricular haemorrhage occurring or extending during study	2 (14)	2 (29)	13 (87)***	5 (100)*
Intraventricular haemorrhage and pneumothorax	1 (17)	1 (14)	12 (80)***	5 (100)*
Intraventricular haemorrhage without pneumothorax	3	2	1	0
Pneumothorax without intraventricular haemorrhage	2	1	0	0
Neither intraventricular haemorrhage or pneumothorax	8 (57)	3 (43)	2 (13)*	0

When compared with treated groups the p values were *≤0.05, **<0.01, ***<0.001

†Intraventricular haemorrhage graded according to Papile *et al* (1978)¹⁵

grade IV; and another control baby from grade II to grade IV.) There were no differences in the incidence of severe intraventricular haemorrhage (grade III or IV) between groups, although the tendency was for the more severe haemorrhages to occur in the control babies. Pneumothorax and intraventricular haemorrhage were associated with each other in controls but not in treated babies (table 4).

Interstitial infiltrates on chest radiography were found more commonly after surfactant instillation (p=0.039), but bacterial cultures from the airways remained sterile for up to seven days.

There were no differences in duration of mechanical ventilation and oxygen treatment in the two groups (table 3). Table 5 shows the causes of death in both groups. Only two babies treated with surfactant died of acute respiratory illness; one after pneumothorax and one with persistent fetal circulation that was unresponsive to tolazoline. This baby was of 26 weeks' gestation and the membranes had been ruptured for five weeks before delivery, making a diagnosis of pulmonary hypoplasia likely, but consent for a postmortem examination was not given. One further treated baby died after the first week from *Pseudomonas* pneumonia and mild

Table 5 Comparison of babies in each group who died in hospital

Gestation (weeks)	Birth weight (g)	Age (days)	Post-mortem examination performed	Cause of death
<i>Treated group</i>				
26	1190	1	+	Hyaline membrane disease, pneumothorax
26	1027	1	—	Pulmonary hypoplasia, persistent fetal circulation
30	1420	19	+	Pneumothorax, pneumonia, pulmonary hypoplasia
<i>Control group</i>				
26	800	1	+	Hyaline membrane disease, pneumothorax, pneumopericardium
27	960	4	+	Hyaline membrane disease, pneumothorax, pneumopericardium, intra-arterial air, intraventricular haemorrhage (IV)
27	1173	8	+	Hyaline membrane disease, pneumothorax, pneumonia
27	875	1	+	Hyaline membrane disease, pneumothorax, intraventricular haemorrhage (IV)
27	1390	7	+	Hyaline membrane disease, pneumothorax, pneumonia, intraventricular haemorrhage (IV)
28	845	4	+	Hyaline membrane disease, pneumothorax
28	1556	6	+	Hyaline membrane disease, pneumothorax, pneumonia
29	1395	3	+	Hyaline membrane disease, pneumothorax, pneumopericardium
31	1550	29	+	Pneumothorax, pneumonia, intraventricular haemorrhage (III), bronchopulmonary dysplasia, periventricular leucomalacia

pulmonary hypoplasia. Hyaline membranes were present at necropsy in one of the babies treated with surfactant and in eight of the controls. Acute respiratory failure or complications such as intraventricular haemorrhage or pneumothorax were the causes of death in all control infants, one baby dying at 29 days of bronchopulmonary dysplasia and post-haemorrhagic hydrocephalus with periventricular leucomalacia.

Discussion

Respiratory distress syndrome remains the major cause of death and disability in preterm infants. For babies who survive the neonatal period handicaps may result from intraventricular haemorrhage and bronchopulmonary dysplasia. As respiratory distress syndrome is due to surfactant deficiency, replacement treatment should be effective, and it is generally agreed that natural surfactants are more effective than synthetic ones in improving the outlook for babies with this disease.^{3 20 21}

Randomised studies of surfactant replacement have been of two types preventive where the surfactant is given at birth to very immature babies,⁵⁻⁹ or interventive where surfactant is given only to babies who are very ill with respiratory distress syndrome.^{4 10 11} Intervention studies have the advantage that all babies entered have respiratory disease, and smaller study numbers may be needed to show beneficial effects. Interventive studies of natural surfactant replacement have shown a reduced incidence of pneumothorax and

death or bronchopulmonary dysplasia in treated infants.^{4 10 11} While there was acute improvement in oxygenation, which lasted from three to six days, there was no reduction in the incidence of intraventricular haemorrhage.^{4 10 11} Only the largest of the preventive studies showed any reduction in intraventricular haemorrhage after treatment.⁵

We found a similar acute improvement in oxygenation which allowed FiO_2 to be reduced in babies treated with surfactant. The difference between the groups remained significant for one week despite a potential bias in our data collection: five of the most severely ill control babies died between 3 and 7 days of age. After 24 hours ventilator settings could also be reduced and this may have accounted for the decreased incidence of pneumothorax in treated babies, especially those weighing less than 1200 g. The reduction in intraventricular haemorrhage may have been due to a combination of improved oxygenation²² and decreased occurrence of pneumothorax^{23 24} as a result of enhanced lung compliance after surfactant treatment. Changes in cerebral blood flow occur in both pneumothorax and intraventricular haemorrhage and merit further investigation.

Although our study design allowed for random allocation of babies into treatment and control groups, there were more treated babies born by caesarean section for severe placental abruption and more control babies born by breech delivery. These differences were not significant and probably not clinically important as babies in both groups had similar Apgar scores and need for intubation at

birth. We also believe that babies in both groups were at similar risk of developing intraventricular haemorrhage and indeed at time of entry into the study similar numbers had grade I and II haemorrhages.

It has been suggested that grade I (or subependymal) and II haemorrhages have a good prognosis and that only grade III and IV haemorrhages are associated with long term neurological handicaps.²⁵ Some reports, however, show that up to 50% of infants with grade II haemorrhages will have mild neurological abnormalities.²⁶ For this reason we believe that our babies treated with surfactant should have an improved long term developmental prognosis when compared with our control infants who were treated with conventional mechanical ventilation. Follow up studies are under way.

Our rates of pneumothorax (80%) and mortality (60%) in the control group were high but they further emphasised the severity of the respiratory distress syndrome in our patients. None of our five control babies of less than 1200 g weight survived. During the study 76 babies weighing <1200 g and without major congenital abnormality had mechanical ventilation for respiratory distress syndrome but only 12 were ill enough to be entered into the trial. Only 11 of the 64 non-study babies died (17%), which compares favourably with the mortality of babies in the treatment group (29%). Our incidence of pneumothorax in a consecutive series of 433 babies treated with mechanical ventilation is 15%.²⁷ Greenough *et al* have reported an incidence of pneumothorax of 100% in babies making expiratory efforts against the ventilator and suggested that use of muscle relaxants prevented this complication.²⁸ Twelve (80%) of our control babies, however, were given muscle relaxants or sedation with diazepam before pneumothorax occurred. If muscle relaxants were used they were always started before the age of 48 hours and most of the pneumothoraces occurred after 48 hours. We had no clinical or radiological evidence of pneumothorax before starting muscle relaxants in any baby in the study.

Not all babies showed sustained improvement after surfactant treatment and all continued to need intensive care and mechanical ventilation for some time. In one study infants needed repeated treatments to sustain effects.⁸ Prophylaxis may be the best method of further reducing the incidence of intraventricular haemorrhage and other complications. The infiltrates observed radiologically in some patients after surfactant replacement can mimic pneumonia and may be due to a form of interstitial reaction to the exogenous material²⁹, we found no evidence of bacterial infection in these babies.

Long term studies on infants treated with surfac-

tant are few^{30 31} and before widespread use of this type of treatment occurs further investigations are needed. The data from the present series of patients, however, indicate that surfactant replacement modifies the clinical course in severe respiratory distress syndrome and reduces the incidence of serious complications.

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Clinical risk factors and periventricular leucomalacia

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SUMMARY Two hundred infants of below 1501 g at birth were regularly examined with real time ultrasound using a 7.5 MHz transducer. Abnormalities were categorised as periventricular haemorrhage (PVH) (n=107) or periventricular leucomalacia (PVL), with or without PVH (n=52). Of the group with PVL, 25 had the appearances of prolonged flare without cavitation. Prospective assessments of up to 50 potential clinical risk factors were made wherever possible on each infant including stratification of all blood gas and systolic blood pressure data. Multivariate logistic regression analyses confirmed a strong correlation between immaturity and PVH but this was not found in cases of PVL. Independent variables associated with PVL included pneumothorax, maximum bilirubin concentration, surgery, and the proportion of time the infant's PaCO₂ remained above 7 kPa. There was a very strong inverse correlation between anaemia and PVL. Systolic blood pressure data were carefully analysed and there was no relation between either hypotension or antepartum haemorrhage and the development of PVL.

Factors predisposing to germinal matrix haemorrhage in preterm infants have been well documented by previous workers by necropsy,¹ computed tomography,² and ultrasound scan diagnosis.³⁻⁸ Periventricular haemorrhage (PVH) is a condition of prematurity related to rupture of capillaries within the germinal matrix; the presence of respiratory distress syndrome and its complications are important associated factors.

The cause of periventricular leucomalacia (PVL) is uncertain. As part of a study using ultrasound to ascertain the incidence and outcome of this condition in 200 very low birthweight infants we prospectively collected data on a large number of potential clinical risk factors for PVL. Statistical analysis of these risk factors was performed to understand further the pathogenesis of this condition.

Patients and methods

Over 16 months (1 January 1984 to 30 April 1985) 200 infants below 1501 g at birth who were admitted to two neonatal intensive care units (Leicester Royal Infirmary and Nottingham City Hospital) had regular cranial ultrasound scans. In both centres an American Technological Laboratories Mark III real time sector scanner fitted with a 3.5, 5, and 7.5 MHz multifrequency scanhead was used. The scans were classified according to the criteria that we have

previously described.⁹ In addition, extensive clinical data relating to antenatal, perinatal, and postnatal events in the first four weeks of life, or until the time of death if this were sooner, were prospectively recorded. The clinical data and scan findings were computerised and statistical analysis performed using a VAX 8600 computer. In one centre (Leicester Royal Infirmary) blood pressure data were measured directly from arterial cannulas or catheters when these were in situ. In infants without arterial access indirect methods were used and only systolic pressure recorded. At the start of this study blood pressure data were not routinely measured in the other centre. This became routine but blood pressure data are incomplete as some infants not requiring intensive care may never have had blood pressure recorded.

Intracranial pathology detected by ultrasound scan was coded as PVH, or PVL, or both. PVL was coded as either 'prolonged flare,' precystic, or cystic as previously described.⁹ The timing of the variables associated with PVH was also coded. The ultrasound appearance of PVL was much more difficult to time accurately, and although recorded, was coded only as present or absent.

DEFINITIONS

Variables were regarded as categorical (mainly dichotomous as shown in table 1), continuous, or

intermittent (table 2). Continuous refers to an absolute value, which varies from infant to infant, and intermittent to all recordings made at variable and non-standard times. The definitions (where not obvious) are listed below.

Pre-eclampsia Diastolic blood pressures above 90 together with proteinuria or oedema, or both.

Antepartum haemorrhage Vaginal bleeding after 20 weeks of gestation and before delivery of the infant. This includes retroplacental clot found at birth.

Fetal distress Type II decelerations detected on antenatal cardiotocography monitoring or meconium staining of the liquor, or both.

Intrauterine growth Weight centile for gestational age derived from the charts of Gairdner and Pearson¹⁰ and Kitchen *et al.*¹¹

Recurrent apnoea Apnoeic episode requiring stimulation or bradycardia, with colour change, or both, and persisting for three days or more.

Persistent ductus arteriosus Characteristic pansystolic murmur together with full peripheral pulses.

Arrhythmias Episodic tachyarrhythmia or bradyarrhythmias documented by observation on electrocardiography. Bradycardia associated with apnoea was excluded.

Necrotising enterocolitis Defined according to the survey criteria of the British Association for Perinatal Paediatrics.¹²

Coagulation disorders Platelet counts of $<20 \times 10^9/l$ or clotting time prolonged three times or more, or both.

Pneumonia Radiological criteria.

Convulsions Clinically evident only and recognised by an experienced observer.

STATISTICAL METHODS

Two binary variables were created that indicated whether the infant developed PVH or whether he developed any evidence of FVL. Analysis of possible risk factors for PVH and PVL was performed separately and in two stages. Initially multiple χ^2 tests were performed on the categorical

Table 1 Categorical data from all infants

Maternal factors	Neonatal factors
Multiple pregnancy	Depression of Apgar score (≤ 5 at five minutes)
Antihypertensive agents	Intubation at birth
β blockers	Race
Methyldopa	White
Pre-eclampsia*	Indian subcontinent
Antepartum haemorrhage*	Others
Prolonged rupture of membranes (>24 hours)	Intrauterine growth*
Fetal distress*	Hypothermia ($\leq 35^\circ\text{C}$ on admission)
Mode of delivery	Recurrent apnoea/bradycardia*
Vaginal	Mechanical ventilation
Caesarean section	Pneumothorax
Place of birth	Alkali infusion
Inborn	Drugs
Outborn	Tolazoline
In utero transfer	Dopamine
	Hypoglycaemia (≤ 1 mmol/l)
	Persistent ductus arteriosus*
	Arrhythmias*
	Congenital heart disease
	Septicaemia (positive blood cultures)
	Exchange transfusion
	Necrotising enterocolitis*
	Surgery (abdominal, duct ligation, or ventriculo-peritoneal shunt)
	Coagulation disorder*
	Pneumonia*
	Hypernatraemia (>150 mmol/l)
	Hyponatraemia (<125 mmol/l)
	Hyperkalaemia (>8 mmol/l)
	High creatinine concentration (>120 mmol/l)
	Anaemia (haemoglobin ≤ 100 g/l)
	Blood transfusion
	Convulsion*

*Defined in the text

Table 2 Coding for continuous and intermittent data with stratification bands set for testing blood gas and systolic blood pressure data points

Continuous data
Gestational age (weeks)
Intrauterine growth (nearest centile)
Maximum bilirubin concentration ($\mu\text{mol/l}$)
Intermittent data
Blood gases
pH (proportion of time <7 , <7.1 , <7.2 , <7.3)
P O ₂ (proportion of time <5 , <7 , <9 , <11 kPa)
P CO ₂ (proportion of time ≥ 9 , ≥ 7 , ≥ 5 , ≥ 3 kPa)
Base deficit (proportion of time <12 , <8 , <4 , mmol/l)
Systolic blood pressure (proportion of time <25 , <35 , <45 , <55 mm Hg)

variables, and Mann-Whitney U tests on the continuous and intermittent variables. The intermittent data were recorded together with the infant's age in hours to allow calculation of the proportion of time the infant was found to be above or below preset

values. In the first analysis previously reported cut off values were used for PaCO_2 (≥ 7.0 kPa⁴) and pH ($< 7.2^{13}$). Subsequently, the blood gas and blood pressure data were stratified by stepwise increments (table 2) and each increment analysed separately as the proportion of time within that stratum. The cut off value that showed the most significant result was then used for further analysis. In the second stage multivariate analyses using generalised linear interactive modelling (GLIM) on all factors found to be significant at the 1% level determined significant factors independently.¹⁴

Results

The median gestational age of the 200 infants was 29 weeks (range 25–37 weeks). PVH occurred in 107 babies (53.5%) and PVL was detected in 52 (26%). Both conditions occurred in 36 (18%) of the study group. Of the infants in the PVL group, 25 of the 52 had the appearances of 'prolonged flare.' Cysts were seen on ultrasound scan within the first week of life in three babies: days 3, 5, and 7, respectively. In addition, echodensity subsequently classified as indicating PVL was present on the initial scan in a further 28 babies.

Categorical and continuous data were available for all 200 infants. Intermittent data in the form of blood gas recordings were made on 171 infants. Twenty nine babies had no respiratory distress and required no supplemental oxygen; blood gases were not measured in this group. Systolic blood pressure data were available from 113 of the infants.

Thirty two of the babies in the study were from multiple pregnancies. In addition, there were five twins and one triplet whose partners were excluded on birthweight criteria. Of these infants, 15 had normal scans, eight developed PVL, and nine had

isolated PVH, of which one was a parenchymal extension.

Fourteen risk factors reached significance ($p < 0.01$) for prediction of development of PVH (table 3) and 10 factors were significantly associated ($p < 0.01$) with the development of PVL (table 4). The results of the stratification analysis for the intermittent data are shown in table 5. For PVH, a pH of < 7.2 , and PaCO_2 of ≥ 7 were found to be the blood gas concentrations that were most strongly associated with haemorrhage. Infants who developed PVH spent a considerably longer proportion of time with blood pressure above 55 mm Hg than those without haemorrhage ($p = 0.0007$). Infants with PVH had significantly higher growth centiles than those without PVH ($p < 0.001$). It seems that there was a reduced risk of PVH in infants with poorer intrauterine growth. When considering PVL, acidosis (pH < 7.1) and hypercap-

Table 4 Risk factors for prediction of development of PVL that reached significance at the 1% level

Gestational age
Anaemia (reduced risk)
$\text{PaCO}_2 \geq 7.0$ kPa
Surgery
pH < 7.1
Maximum bilirubin concentration
Coagulation disorder
Number of blood transfusions
Intermittent positive pressure ventilation
Pneumothorax

Table 5 Analysis of the proportion of time spent with intermittent data point results in each stratification band. Analysis by Mann-Whitney U test

	Periventricular leucomalacia	Periventricular haemorrhage
Ph		
< 7.0	$p = 0.02$	$p = 0.005$
< 7.1	$p = 0.002$	$p = 0.003$
< 7.2	NS	$p = 0.01$
< 7.3	NS	NS
PaO_2 (kPa)		
	NS for any strata	NS for any strata
PaCO_2 (kPa)		
≥ 9	$p = 0.009$	$p = 0.002$
≥ 7	$p = 0.004$	$p = 0.01$
≥ 5	NS	NS
≥ 3	NS	NS
Base deficit (mmol/l)		
< -12	NS	$p = 0.03$
< -8	NS	$p = 0.02$
	NS for other strata	NS for other strata
Systolic blood pressure		
> 55 mm Hg	NS	$p = 0.0007$
	NS for other strata	NS for other strata

Table 3 Risk factors for prediction of development of PVH that reached significance at a 1% level

Gestational age
Poor intrauterine growth (reduced risk)
Anaemia (reduced risk)
Coagulation disorder
Vaginal delivery v caesarean section
pH < 7.2
Arrhythmia
Need for blood transfusion
Intermittent positive pressure ventilation
Tolazoline infusion
Alkali infusion
$\text{PaCO}_2 \geq 7.0$ kPa
Surgery
Systolic blood pressure > 55 mm Hg

Table 6 *Significance for the risk factors associated with periventricular haemorrhage and periventricular leucomalacia. (The estimate refers to the GLIM equation)*

	Estimate	Standard error of the estimate	p Value
Periventricular haemorrhage			
Gestation	-0.414	0.0937	<0.001
Anaemia	-1.845	0.4374	<0.001
Coagulation disorder	+1.935	0.7047	0.001
Proportion of time $\text{PaCO}_2 \geq 7$ kPa	+2.770	1.3970	0.038
Periventricular leucomalacia			
Anaemia	-1.860	0.4907	<0.001
Maximum bilirubin concentration	+0.013	0.0041	<0.001
Pneumothorax	+1.556	0.5149	0.001
Proportion of time $\text{PaCO}_2 \geq 7$ kPa	+3.649	1.3270	0.005
Surgery	+1.305	0.5700	0.022

nia ($\text{PaCO}_2 \geq 7$) were the only two intermittent items to reach significance at a 1% level.

Multivariate logistic regression analyses were performed on the 14 risk factors for PVH and the 10 for PVL. The GLIM equation for PVH can be described as: $\log P/1-P = 12.27 - 0.414a - 1.845b + 1.935c + 2.770d$ and for any degree of PVL as: $\log P/1-P = -3.50 - 1.860b + 1.556e + 0.013f + 3.649d + 1.305g$ where a =gestational age in weeks; $b=1$, if haemoglobin <100 g/l at any time, otherwise 0; $c=1$, if any clotting disorder, otherwise 0; d =proportion of time $\text{PaCO}_2 \geq 7$; $e=1$, if pneumothorax, otherwise 0; f =maximum bilirubin level, and $g=1$, if any surgical procedure, otherwise 0.

This means that the risk of developing PVH was negatively correlated with advancing gestational age and anaemia (haemoglobin <100 g/l). PVL was also negatively correlated with anaemia. Table 6 summarises these independent variables for both PVH and PVL.

These models were derived from the 171 infants with complete blood gas data. When the model for PVH was applied to the 115 infants with systolic blood pressure data it did not significantly improve the fit of the model. Further analyses were performed to distinguish whether there were different risk factors for cystic and precystic PVL compared with prolonged flare alone. Three factors best predicted both these conditions: these were anaemia (negative correlation), pneumothorax, and maximum bilirubin concentration.

Discussion

The risk factors for PVH in the newborn are well

documented, and although a large number of variables have been reported to predispose to haemorrhage, many studies have agreed on a relatively few commonly associated conditions. These include respiratory distress syndrome,^{3-5,7} pneumothorax,^{5,7} acidosis,³⁻⁵ hypercapnia,^{4,5,7} and coagulation disorders.^{5,15} There are considerably less data available concerning the risk factors predicting the onset of PVL. As cystic PVL is now known to be associated with adverse neurodevelopment the purpose of this study was to identify the events that predisposed to PVL and to compare these with those preceding haemorrhage.

Many of the risk factors that we found on multivariate analysis to predispose to PVH were similar to those previously reported by others. There was an extremely strong association between prematurity and PVH, which is not unexpected as the germinal matrix tends to involute with increasing maturity. Clotting disorders and hypercapnia are also well recognised factors. The basic cause of PVH is rupture of the capillaries within the germinal matrix, probably in response to acute fluctuations in cerebral blood flow. Mechanical ventilation and fluctuating blood pressure, hypercapnia, and acidosis may predispose to the acute changes in cerebral blood flow, and minor bleeding in the presence of a clotting disorder may cause more extensive haemorrhage into the lateral ventricle.

To date three studies have been published reporting the aetiological factors associated with PVL.¹⁶⁻¹⁸ Maternal antepartum haemorrhage was found to be an important risk factor in all three studies, but did not reach significance in our analysis. In addition, birth asphyxia,^{16,17} recurrent apnoea,¹⁶ patent ductus arteriosus,¹⁶ speticeaemia,¹⁶ seizures,¹⁶ duration of mechanical ventilation,^{16,18} and hypocarbia ($\text{PaCO}_2 < 3.3$ kPa¹⁸) were all found in previous studies to have a significant association with PVL.

Sinha *et al* postulated that hypotension arising from a variety of perinatal insults may have been the common pathway to the development of PVL, but they reported no blood pressure measurements in their study.¹⁶ Although we regularly measured blood pressure in sick infants we were surprised to find as Weindling *et al* had previously reported,¹⁷ that there was no correlation between hypotension and PVL. It is of interest, however, that infants who developed haemorrhage had a systolic blood pressure of less than 55 mm Hg for a significantly shorter proportion of time than those infants without haemorrhage. Before dismissing blood pressure as unimportant in the development of PVL a study using direct and continuous blood pressure recordings would be valuable. We have seen extensive PVL develop in infants with a good central blood

pressure at all times, and it has been suggested that PVL may be due to uncoupling between the metabolic requirements of the periventricular white matter and its local perfusion.¹⁹ This attractive proposition requires further evaluation.

Our study differed from the others by enrolling a larger number of very low birthweight infants, the prospective nature of the data collection, and the multivariate regression analysis performed on the risk factors. Unlike the other studies we found ventilatory complications (pneumothorax and hypercapnia) to be independently associated with the diagnosis of PVL. The importance of hyperbilirubinaemia is of interest but is difficult to explain. We are not aware of any reports suggesting neurotoxicity of bilirubin to the periventricular white matter. Of the 13 infants who underwent surgery before the development of PVL, an abdominal operation for necrotising enterocolitis was the commonest underlying cause of the surgical procedure (seven babies). Necrotising enterocolitis has been associated with the late onset of PVL in some infants,²⁰ but in our study necrotising enterocolitis did not reach significance as a risk factor. Infants undergoing surgery were probably among the sickest babies and therefore the most likely to develop cerebral insults.

There was an inverse relation between anaemia and the development of both PVH and PVL. The reason for this is probably related to our policy of transfusing the sickest infants more frequently than less ill babies, thereby preventing this high risk group from becoming anaemic. Those infants who were less ill were allowed a lower concentration of haemoglobin and this is the group least likely to develop intracranial complications.

We have previously reported that PVH and PVL commonly occur in the same infant,⁹ and this study has found that haemorrhage and PVL shared eight risk factors that reached significance on univariate analysis. These lesions seem most likely to occur in the sickest infants, but interestingly, although immaturity was very closely related to the frequency of haemorrhage, it was not associated with the onset of PVL. Although the risk of PVH reduces with increasing gestational age, the infant's brain may remain susceptible to PVL for a longer period of time.

We recommend caution in the interpretation of the findings of this study and other similar papers on perinatal risk factors of PVL for two reasons: because of the limitation of multiple significance testing, which may produce spurious results; and secondly, PVL may be the result of a variety of quite disparate factors. Lumping them all together may well obscure some of the occasional but nevertheless

important causal factors. There are babies in this study who sustained cardiac arrhythmia with hypotension and who subsequently developed PVL shortly afterwards.²¹ It is also possible that imprecise methods for detecting some conditions, such as fetal distress, may produce a false negative result for this variable. Because these associations were rarely seen they may not have reached significance in our cohort.

Finally, our analysis has shown that the risk factors for prolonged flare are similar to those for PVL. We have previously suggested, on the basis of pathological and ultrasound correlation, that prolonged flare is part of the milder end of the PVL range.²² Our analysis of associated factors reported here confirms that the same risk factors operate for both prolonged flare and cystic or precystic PVL; this adds further weight to our hypothesis that prolonged flare is not an artefactual appearance. We must await follow up data on infants with this condition to establish its prognostic importance.

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Centralisation of treatment and survival rates for cancer

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SUMMARY Between 1977 and 1984 the proportion of children with malignant disease in Britain initially referred to specialist paediatric oncology centres increased from 44% to 71%. The percentage varied considerably with type of disease and region of residence. Children with acute non-lymphoblastic leukaemia, non-Hodgkin's lymphoma, Ewing's tumour, rhabdomyosarcoma, and (during 1981–84) osteosarcoma treated at paediatric oncology centres had significantly higher survival rates than those treated elsewhere. Children with cancer should be referred to specialist centres so that they may benefit as early as possible from the latest advances in treatment.

Since the 1960s there has been an increasing trend towards centralisation of the treatment of childhood cancers in Britain. In 1977 the United Kingdom Children's Cancer Study Group (UKCCSG) was formed by a number of consultants specialising in paediatric oncology. Since then there has been a steady increase in membership of the UKCCSG until now nearly every Health Service region in Britain contains a paediatric oncology centre whose senior staff are members of the UKCCSG. This paper describes the increased centralisation of the care of children with cancer since 1977, and compares survival rates for children with some of the principal types of childhood neoplasm who were treated at paediatric oncology centres with those of children treated elsewhere.

Patients and methods

The Childhood Cancer Research Group (CCRG) maintains the national registry of childhood malignant diseases for Great Britain. The primary source of information is notification to the National Cancer Registration schemes for England, Scotland, and Wales; the CCRG receives a copy of the registration of each patient aged under 15 years.

Since July 1977 the UKCCSG has kept a register of all children with malignant disease who are either under the continuing care of one of its members or whose management is shared with consultants in district general hospitals. The CCRG receives copies of all notifications to this register. By 1984 there were UKCCSG centres in the following cities

and towns in Great Britain: Aberdeen, Birmingham, Bristol, Cambridge, Cardiff, Edinburgh, Glasgow, Leeds, Leicester, Liverpool, London (two), Manchester, Newcastle upon Tyne, Nottingham, Sheffield, Southampton, and Sutton. There were also centres in Belfast and Dublin whose patients are not included in the present analyses.

Confirmation of the diagnosis and information on follow up are obtained for children in both registries about five years after diagnosis. The CCRG also routinely receives death certificates for people under the age of 20 dying of neoplasms. Survivors are flagged in the National Health Service Central Registers so that the CCRG is notified of any deaths or embarkations (resulting in loss to follow up). Most survivors in both the CCRG and UKCCSG registries have been followed up at least until the end of June 1986.

Although cancer registration in Britain is population based, it is not quite complete. The proportion of all patients in Britain who are managed at paediatric oncology centres, however, may be estimated as the proportion of the total number of children with a cancer registration who also have a UKCCSG notification.

Comparisons of survival rates between UKCCSG patients and non-UKCCSG patients were made for eight of the principal types of childhood neoplasm: acute non-lymphoblastic leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, Wilms' tumour, osteosarcoma, Ewing's tumour, and rhabdomyosarcoma. All children in these groups were categorised by the type of treatment centre

responsible for their main treatment. Paediatric oncology centres (this group includes children whose treatment is shared between the main centre and another); other teaching hospitals and other non-teaching hospitals.

Some hospitals began to participate in the UKCCSG after 1977. For the present analyses, patients at these centres were counted as being treated at other teaching hospitals if diagnosed before consultants at the centre became members of the UKCCSG and as being treated in paediatric oncology centres if diagnosed since their participation in the UKCCSG began.

Actual survival rates and the significance of differences between survival curves were calculated using standard methods.¹ The effect of referral on survival rates for childhood acute lymphoblastic leukaemia is the subject of another study (Stiller and Draper, unpublished observations) and is therefore not considered in detail in the present paper.

Results

Table 1 shows the estimated percentages of children with cancer in Britain during the period July 1977 to December 1984 who were initially referred to

Table 1 *Percentages of children with malignant neoplasms initially referred to paediatric oncology centres 1977-84*

Diagnostic group and age (years)	Years of diagnosis	
	July 1977-1980	1981-84
Acute lymphoblastic leukaemia	64	78
Acute non-lymphoblastic leukaemia	62	77
Other leukaemia	49	54
Hodgkin's disease	60	67
Non-Hodgkin's lymphoma	67	77
Neuroblastoma	73	86
Wilms' tumour	69	88
Retinoblastoma	11	27
Medulloblastoma	45	56
Other central nervous system	25	31
Osteosarcoma	36	52
Ewing's tumour	56	73
Rhabdomyosarcoma	55	90
Malignant germ cell tumour	51	62
Other malignant disease	41	44
Age		
0-4	55	72
5-9	58	67
10-14	45	53
Total	55	65

paediatric oncology centres. The proportion of such children increased from 44% in the second half of 1977 to 71% in 1984. This increase took place for children of all ages, but throughout the period a smaller proportion of children aged 10-14 (and especially of those aged 12 and over) were referred to a paediatric oncology centre. The referral rates varied considerably between health regions, ranging in England from 85% for children living in the North West to 28% for those living in Oxford. The rates also varied with diagnostic group from over three quarters for the leukaemias, neuroblastoma, Wilms' tumour and rhabdomyosarcoma to slightly over one quarter for central nervous system tumours other than medulloblastoma. A large proportion of children with retinoblastoma have been treated at two London hospitals (Sanders and Draper, unpublished observations), but until recently these patients were not notified to the UKCCSG.

Table 2 shows the total numbers of patients included in the analyses of survival categorised by type of treatment centre. Children who are in the UKCCSG register but for whom a cancer registration has not yet been received are included in these analyses. Children who died before treatment could be given, including some where the diagnosis was made at necropsy, have been excluded.

For many of the non-UKCCSG children diagnosed from 1981 onwards the diagnosis was based solely on the cancer registration and in a few instances may be changed when the five year follow up is completed. Moreover, registration of non-UKCCSG children for 1981-84 is incomplete. For these reasons the analyses have been carried out separately for children diagnosed in 1977-80 and in

Table 2 *Total numbers of patients included in survival analysis for each diagnostic group categorised by type of treatment centre*

Diagnostic group	Treatment centre			Total
	Paediatric oncology centre	Other teaching	Other non-teaching	
Acute non-lymphoblastic leukaemia	295	54	40	389
Hodgkin's disease	291	81	63	435
Non-Hodgkin's lymphoma	385	56	56	497
Neuroblastoma	417	45	24	486
Wilms' tumour	397	44	42	483
Osteosarcoma	108	71	61	240
Ewing's tumour	158	49	27	234
Rhabdomyosarcoma	284	35	32	351
Total	2335	435	345	3115

Table 3 Actuarial three year percentage survival rates for children at each type of treatment centre with results of log rank tests for heterogeneity of survival curves among types of treatment centre allowing for age and year of diagnosis

Diagnostic group	Treatment centre and years of diagnosis						χ^2 (2 df)	p value
	Paediatric oncology centre		Other teaching		Other non-teaching			
	1977-80	1981-84	1977-80	1981-84	1977-80	1981-84		
Acute non-lymphoblastic leukaemia	28	32	23	(21)	9	(6)	8.29	<0.05
Hodgkin's disease	90	98	91	85	88	100	0.69	NS
Non-Hodgkin's lymphoma	56	70	32	(56)	43	(58)	10.8	<0.01
Neuroblastoma	32	49	52	(54)	(25)	*	4.09	NS
Wilms' tumour	83	80	81	(77)	81	*	0.31	NS
Osteosarcoma	39	54	32	24	38	37	4.39	NS
Ewing's tumour	46	50	24	(33)	(43)	(45)	8.04	<0.05
Rhabdomyosarcoma	63	63	25	(36)	46	*	21.0	<0.001

Figures in parentheses are percentages of fewer than 20 patients, * = fewer than 10 patients in the group

1981-84. This also enabled trends in survival to be examined, allowing for changes in referral patterns. Because older children were less likely to be treated at paediatric oncology centres, age at diagnosis grouped as 0-11 and 12-14 years was allowed for in all the analyses.

Table 3 shows the three year survival for children in each diagnostic group, categorised by year of diagnosis and treatment centre, together with the results of significance tests for differences in the survival curves among types of treatment centre, allowing for the effects of age and year of diagnosis.

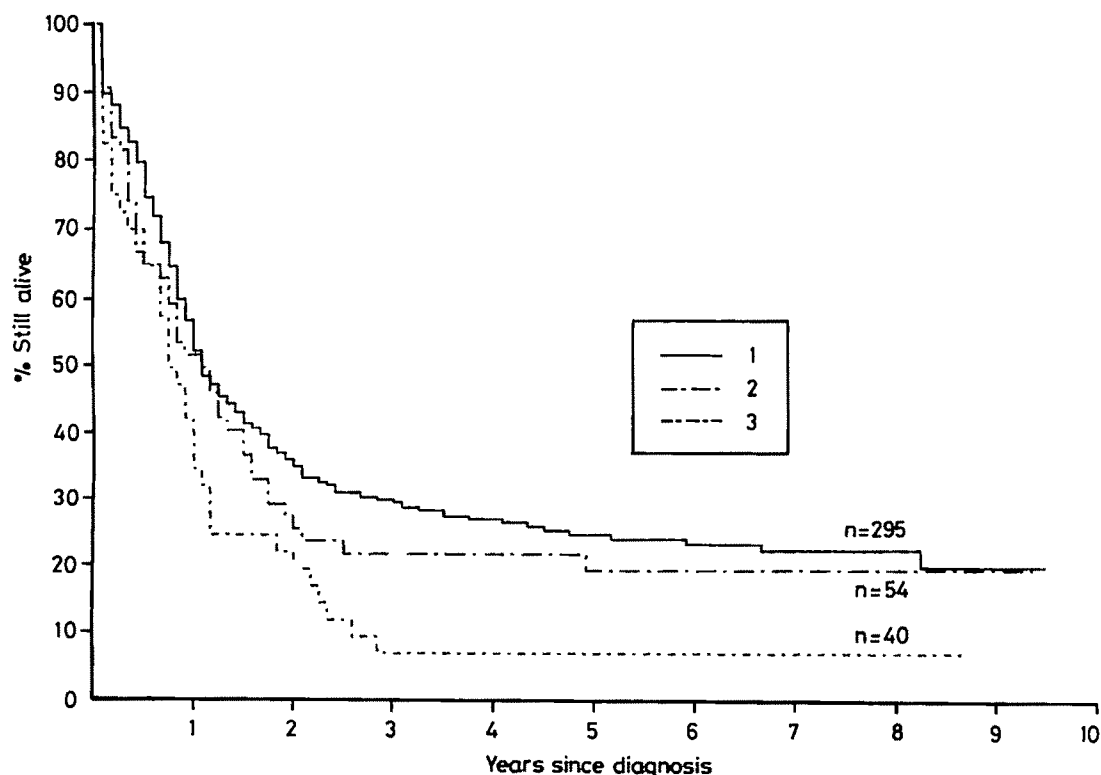


Fig 1 Actuarial survival curves for children with acute non-lymphoblastic leukaemia classified by type of treatment centre 1=Paediatric oncology centres; 2=other teaching hospitals, 3=other hospitals

Fig 1 shows the significant variation among types of treatment centre in the survival for children with acute non-lymphoblastic leukaemia. This difference held for both age groups and in both calendar periods and was largely accounted for by the low survival among children in the non-teaching hospitals.

The survival for children with Hodgkin's disease was high with over 90% expected to survive at least three years, and there was no evidence of variation among types of treatment centre. Between 1977-80 and 1981-84 there was evidence of further improvement in the already high survival rate.

There was a highly significant difference in survival in non-Hodgkin's lymphoma among the types of treatment centre, with the highest rates being seen at paediatric oncology centres. This difference held for both age groups. There was a marked increase in survival between 1977-80 and 1981-84 among children treated at paediatric oncology centres and elsewhere, but the rates for other hospitals during 1981-84 only reached those

attained at the paediatric oncology centres during 1977-80 (fig 2).

Analysis of the survival for neuroblastoma showed no clear heterogeneity among types of treatment centre. Tumour stage according to the Evars system² was given for most of the patients, however, and the paediatric oncology centres had a considerably higher proportion of stage III and IV patients (who have a worse prognosis) than other hospitals. At paediatric oncology centres there was a substantial improvement in survival rates between 1977-80 and 1981-84. Three year survival at these centres increased from 32% to 49% between the two calendar periods for all stages combined, from 33% to 61% for stage III, and from 11% to 21% for stage IV.

There was no difference in survival for Wilms' tumour among types of treatment centre even allowing for the fact that children with metastatic disease at diagnosis appeared to be more likely to be referred to a paediatric oncology centre, nor was there any change between 1977-80 and 1981-84.

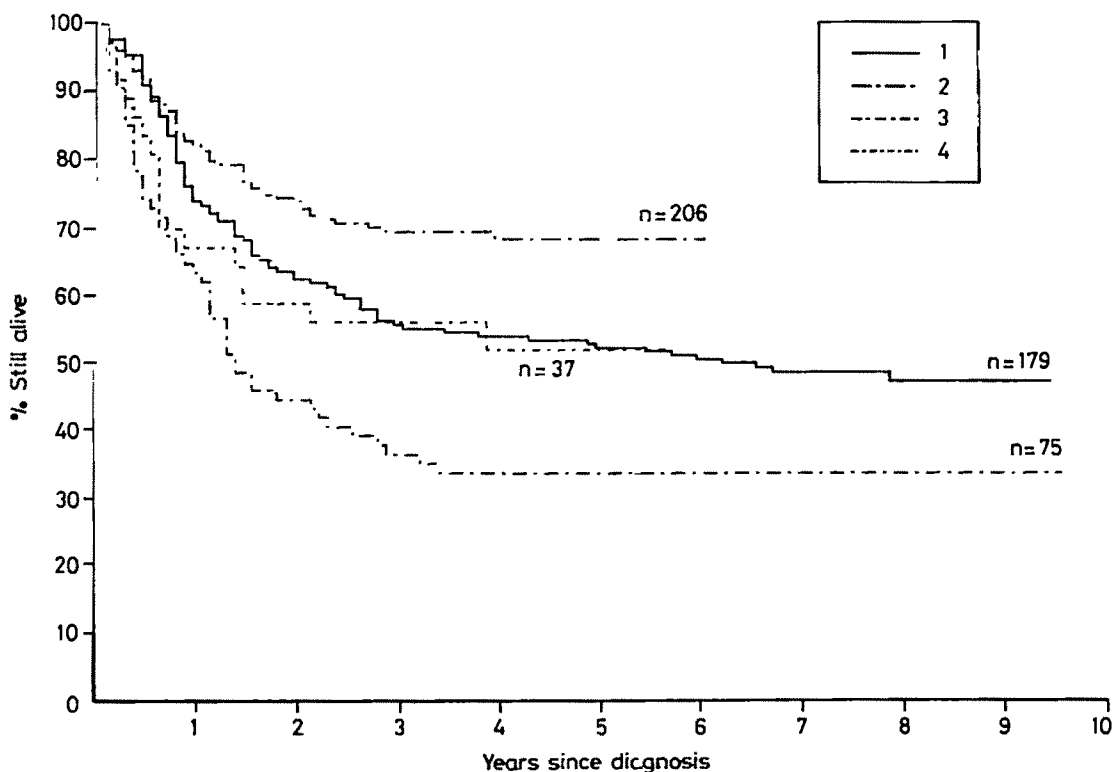


Fig 2 Actuarial survival curves for children with non-Hodgkin's lymphoma classified by type of treatment centre 1=Paediatric oncology centres, 1977-80, 2=paediatric oncology centres, 1981-4, 3=all other hospitals, 1977-80; 4=all other hospitals, 1981-4.

During 1977–80 survival for childhood osteosarcoma was similar in all types of treatment centre, with rates of about 36% at three years and slightly under 30% at five years. For 1981–84, there was a significant variation, with children treated at paediatric oncology centres having a considerably higher probability of survival. The survival for the children at these centres in this period showed a definite increase over earlier years (fig 3); there was little evidence of a corresponding improvement elsewhere.

There were significant differences among types of treatment centre in survival for Ewing's tumour, with a greater proportion of children surviving at paediatric oncology centres. The prognosis for Ewing's tumour varies with primary site, being best for tumours in the long bones of the limbs and worst for those in the ribs and pelvis. In the analysis of survival by site of tumour there was a significant variation among types of treatment centre for patients with primaries in both of these sites and in the miscellaneous other sites—in each case with a

higher survival rate at the paediatric oncology centres. These centres treated proportionally more patients with prognostically unfavourable primary sites. There was no evidence of any substantial improvement in overall survival between 1977–80 and 1981–84.

There was a significant variation in the survival for rhabdomyosarcoma, again with a higher proportion of survivors at paediatric oncology centres (fig 4). This was true for both age groups and both calendar periods. There was no evidence of an increase in survival rates between 1977–80 and 1981–84.

Discussion

The benefits of referral to specialist treatment hospitals for patients with cancer have been widely discussed.^{3,4} For children there has until recently been little published about the advantages of treatment in specialist centres, but in the past decade four papers have reported beneficial effects on

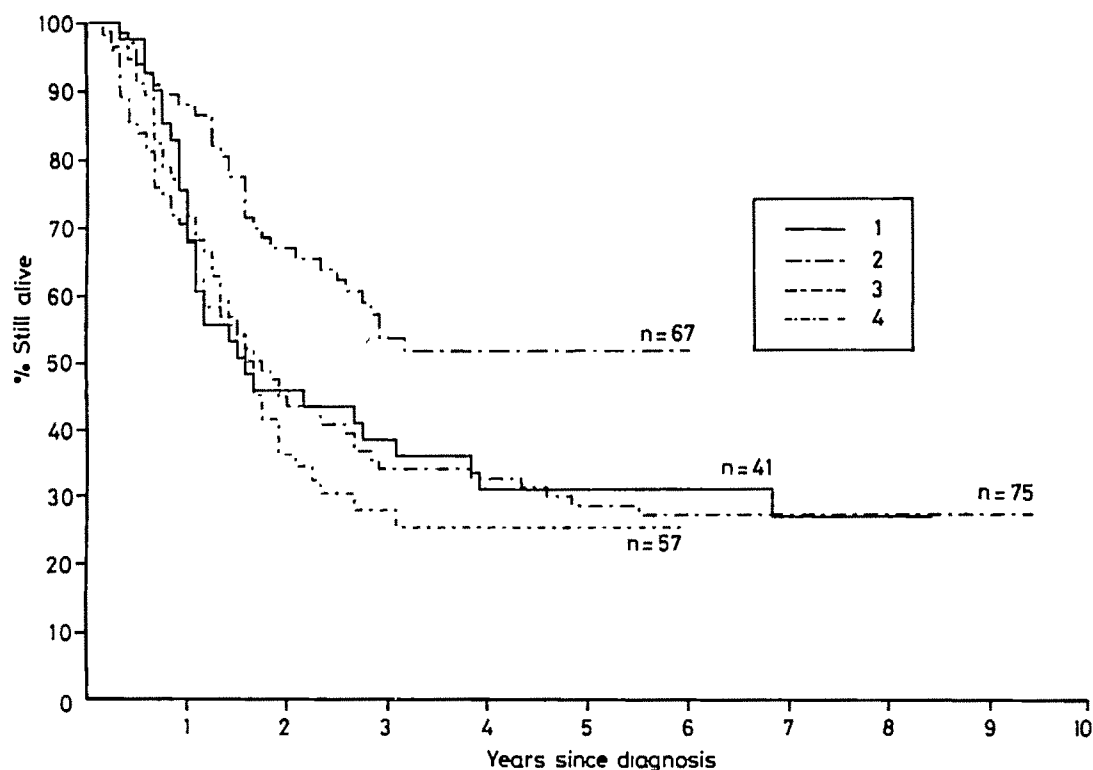


Fig 3 Actuarial survival curves for children with osteosarcoma classified by type of treatment centre. 1=Paediatric oncology centres, 1977–80; 2=paediatric oncology centres, 1981–4; 3=all other hospitals, 1977–80; 4=all other hospitals, 1981–4.

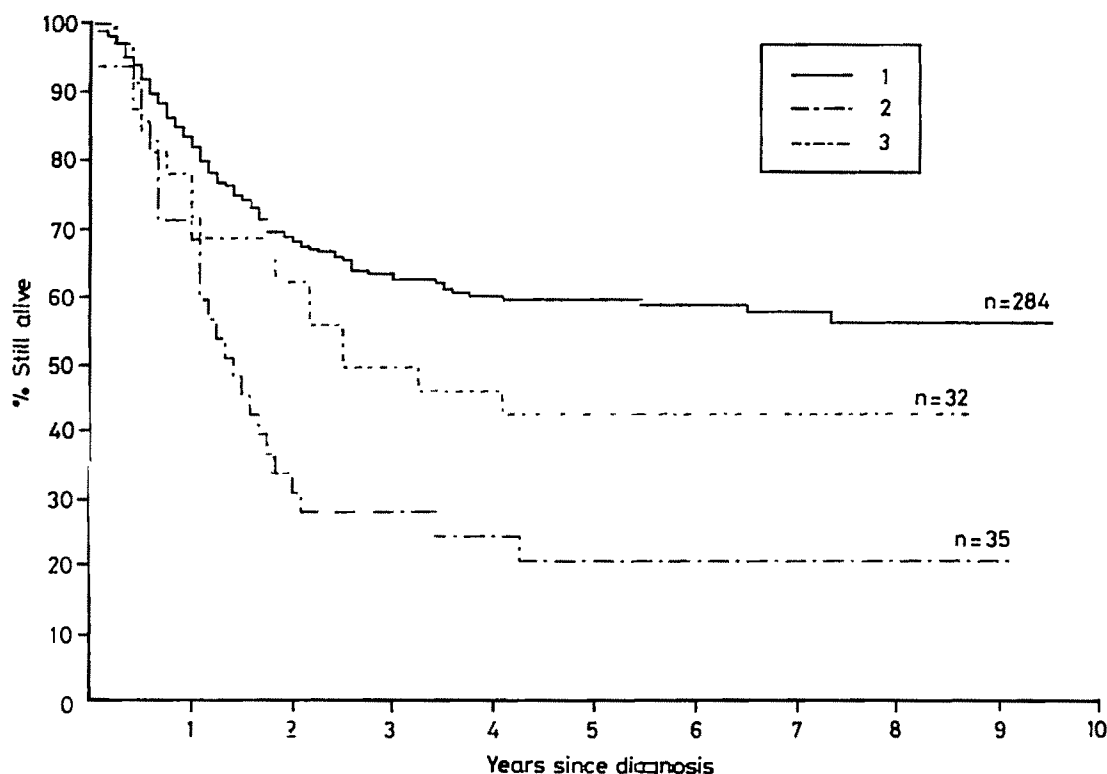


Fig 4 Actuarial survival curves for children with rhabdomyosarcoma, classified by type of treatment centre 1=Paediatric oncology centres, 2=other teaching hospitals, 3=other hospitals

survival when treatment was given according to standardised protocols for children with Wilms' tumour,^{5,6} acute lymphoblastic leukaemia,⁷ and medulloblastoma.⁸ Kramer *et al* examined the effect of place of treatment on the survival for children with Wilms' tumour, rhabdomyosarcoma, and medulloblastoma in the population based Greater Delaware Valley Pediatric Tumor Registry.⁹ A recent analysis of data about acute lymphoblastic leukaemia in Britain during the 1970s (Stiller and Draper, unpublished observations) showed that survival was higher among children who were included in nationally organised trials or referred to specialist centres treating large numbers of patients.

In Britain there has been well established national cooperation in trials of treatment for acute lymphoblastic leukaemia, coordinated by the Medical Research Council since the 1960s.¹⁰ The Council also supported trials in the treatment of Wilms' tumour,¹¹ and a few of the largest children's hospitals took part in some of the studies of other childhood cancers organised by the International

Society of Paediatric Oncology, but in general there was no formal basis in Britain for national collaborative studies of the treatment of childhood cancer until the formation of the UKCCSG. The data presented here show that since 1977 there has been a definite trend towards treatment of children with malignant disease in paediatric oncology centres, with UKCCSG members now being responsible for at least two thirds of newly diagnosed patients.

The survival analysis showed a much lower survival for patients with acute non-lymphoblastic leukaemia treated at non-teaching hospitals, possibly because they would have had little experience in treating children with this disease. Although the prognosis is still poor, the three year survival of about 26% during 1977-84 was considerably higher than the 10% for 1971-74.¹² This improvement is largely attributable to the adoption of more effective chemotherapy, though bone marrow transplantation may have also increased the number of survivors.

By the early 1970s Hodgkin's disease was already one of the childhood cancers with the best prognosis, with a three year survival of over 80%.¹²

Since then there has been further steady improvement, and nowadays well over 90% of patients survive for at least three years. These improvements are similar to those achieved in adults during the same period.¹³

There has been a considerable improvement in survival for childhood non-Hodgkin's lymphomas since 1971-74 when the three year survival was only 28% compared with over 65% for patients diagnosed in the 1980s.¹² The adoption of more intensive multiple drug regimens is probably responsible for the greatly improved outlook.^{14 15}

Although survival rates for neuroblastoma are still low in comparison with many other childhood cancers, the prospects are much better than in the early 1970s when long term survival was only 15%.¹² The survival was lower at paediatric oncology centres than elsewhere, maybe because these centres were seeing a much larger proportion of patients with advanced disease. The greater number of patients with stage III and IV tumours at these centres could be an artefact caused by more careful staging than at other hospitals, but this is unlikely as the proportions of patients in these stages at the paediatric oncology centres remained constant between the two calendar periods (at around 19% for stage III and 54% for stage IV), and most of the survivors at other hospitals had localised tumours which were apparently cured without chemotherapy. During the past decade there have been considerable improvements in the treatment of advanced neuroblastomas at specialist centres with encouraging results; more patients have been treated with chemotherapy regimens that include cisplatin and melphalan.¹⁶

Survival rates everywhere were high for Wilms' tumour compared with that of earlier years. Previous reports showed an advantage in survival for patients treated in clinical trials or at specialist centres.^{5 6} There was no significant difference in survival in the present series between children managed at paediatric oncology centres and those managed elsewhere. Although some of the children in other hospitals have been included in the UKCCSG study and treated using that protocol, however, it seems that others were given more radiotherapy or chemotherapy than was appropriate for their stage and histological subtype within the study. Kramer *et al* also found no significant differences in survival between cancer centres and other hospitals.⁹ They suggested that this might be because by the time of their study Wilms' tumour was readily curable by regimens that had been published and were widely used.

Survival rates for childhood osteosarcoma in 1977-80 showed a modest improvement over

1971-74, possibly because most of the patients diagnosed in the more recent period received adjuvant chemotherapy. There was a much greater improvement for 1981-84 but this was limited to children managed at paediatric oncology centres. Detailed information is not yet available, but more effective chemotherapy might have been given at these centres while other hospitals were continuing with earlier regimens.

Overall survival for Ewing's tumour showed no change during 1977-84, and indeed was no higher than for patients diagnosed during 1971-74 (51% at three years).¹² There was, however, a highly significant variation among types of treatment centre in favour of the paediatric oncology centres. Children treated at other hospitals usually received both radiotherapy and chemotherapy in similar combinations to those used at paediatric oncology centres.

The survival rate for rhabdomyosarcoma showed a definite improvement over 1971-74 (28% at three years)¹² but there was little evidence of further advances within the period under review. Again the survival rates for the paediatric oncology centres were superior to those elsewhere, a result similar to that reported by Kramer *et al* in the United States.⁹ There were a few patients at other hospitals who initially had radiotherapy but no chemotherapy, but most appeared to have received standard combinations of cytotoxic drugs.

Details about doses and duration of chemotherapy were not generally available in the registry. The poor survival rates at other hospitals for Ewing's tumour and rhabdomyosarcoma, which are often treated using similar combinations of chemotherapy, however, suggest that although appropriate drugs were used they may not always have been given in adequate doses.

Analyses of survival rates based on registration data are susceptible to various sorts of bias. In removing the untreated patients and stratifying the rest by age, year of diagnosis, and where appropriate primary site, however, the most important confounding factors should have been allowed for in comparing the rates for patients referred to different types of treatment centre.

For certain diagnostic groups, notably acute non-lymphoblastic leukaemia and non-Hodgkin's lymphoma, there was a considerably higher initial mortality at the non-specialist centres, suggesting failure to achieve remission. Despite the exclusion of untreated patients from the survival analyses, a few patients might have been diagnosed too late for referral to a paediatric oncology centre but nevertheless received some treatment at other hospitals. This is unlikely to account for the difference

between types of treatment centre, however, because when the analyses were repeated with all children who survived under one month excluded, the significance level of the difference in survival did not change for any diagnostic group.

There have been considerable improvements in recent years in the survival for several types of childhood cancer, presumably resulting from advances in treatment, and the results obtained at specialist paediatric oncology centres have tended to be better than those achieved elsewhere. The results presented here underline the importance of referring patients to specialist centres where they may benefit as early as possible from the latest advances in treatment. In some instances children receive less aggressive treatment than previously, still with a high probability of survival but with a reduced risk of long term sequelae. Centralisation of treatment may result in increased cost to the family¹⁷ and a greater workload at the paediatric oncology centres, but these disadvantages can be alleviated by closer cooperation between specialist centres and local hospitals especially during maintenance therapy.

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Paediatric intensive care in a district general hospital

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SUMMARY Five years' experience of paediatric intensive care in a district general hospital were analysed retrospectively. A total of 54 infants and children required respiratory support during this time—21 on a high dependency area of the children's ward and 33 on a general intensive care unit. Forty two (78%) of the patients survived, and 33 (61%) of the patients required respiratory support within four hours of admission, thus the experience of the local paediatric and anaesthetic team was crucial to the management of these children. Good intensive care for children can be provided within a district general hospital.

In most district hospital paediatric units the numbers of critically ill children admitted are small and are not sufficient to justify the setting up and staffing of separate paediatric intensive care areas. In such hospitals, however, there has to be provision for the resuscitation and intensive care of critically ill children. In Northampton, as in many districts, such care is provided in two areas within the general hospital: in a high dependency area of the general paediatric ward and on the general intensive care ward. We describe the results of five years' experience of providing care for children in this manner.

Background

Northampton General Hospital is a district hospital of 700 beds providing acute services for south Northamptonshire and serving a total population of 301 400 (1986) of which 59 700 are children. The paediatric unit has 56 beds, including several cubicles which can be adapted for intensive care; there is also a neonatal unit of 28 cots with four intensive care cots. Medical staff comprises three consultants, a senior registrar, a registrar, and five senior house officers. The general intensive care unit has seven beds two of which are in side rooms off the main intensive care area. Medical staff comprise two consultant anaesthetists, who specialise in intensive care, and two senior house officers in anaesthetics who alternate 24 hour cover. On the children's ward medical care is provided by the paediatric team with the anaesthetic team advising on request. Nursing care is provided by the general ward staff most of whom are trained as registered sick children's nurses. On the intensive care unit care is shared between the anaesthetic and paediatric teams; most

of the nurses have specific intensive care training but not paediatric training.

The decision to admit to either area for intensive care depends on several factors including age (infants are generally cared for on the children's ward), place of resuscitation, and workload and staffing levels in the two areas. The need for referral to a tertiary centre is assessed on an individual basis. We would usually refer neurosurgical problems, particularly head injuries, complicated neurological problems, and renal problems requiring dialysis.

Equipment in the intensive care areas and investigation facilities within the hospital comply with the main recommendations of the British Paediatric Association working party on paediatric intensive care.¹ We are able to provide full respiratory support; perform electrocardiography, monitor the respiratory rate, arterial and venous pressure; measure blood and transcutaneous oxygen and carbon dioxide concentrations; and we can deliver long term total parenteral nutrition. We do not have the ability to monitor intracranial pressure and, at present, patients have to be transferred to a referral centre for computed tomography.

Methods

The care of all paediatric patients who received intensive care during the five years between 1 January 1982 and 31 December 1986 was analysed in retrospect. A paediatric patient was defined as being less than 14 years old; intensive care was defined as the treatment of any child who required maintenance by an artificial airway or by artificial ventilation. As an indication of the paediatric workload of a general intensive care unit we

included children who were admitted to the intensive care unit for observation but who did not require respiratory support.

Results

A total of 54 patients needed airway or ventilatory support, or both during the five years. This represents 0.6% of all paediatric admissions, which totalled 8924 during this time. Altogether, 21 infants (39%) were managed on the children's ward, their mean age was 7.25 months (range 17 days to 19 months). Thirty three infants and children (61%) were managed on the general intensive care unit; their mean age was 4.9 years (range 8 weeks to 13.5 years), of these only two were less than 1 year old. Seventeen additional children were observed on the intensive care unit but did not require respiratory support; their mean age was 3.7 years (range 1 year to 11.25 years). These 50 patients represented 3.8% of the total of 1307 admissions to the intensive care unit.

The mean time between admission and intubation was 11.5 hours (range 0–144 hours). In 21 cases (39%) intubation was required within one hour of admission, 33 (61%) required intubation within four hours of admission. Of those requiring resuscitation in the first four hours, 28 went to the intensive care unit and five went to the children's ward. The mean amount of time spent on respiratory support was 100 hours (range 12–576 hours). The diagnostic categories and details of the children are shown in the table.

Thirty two patients had primarily respiratory problems. The 14 cases with upper respiratory problems all made a full recovery, and of the 18 cases with lower respiratory problems 16 made a full recovery. One child with measles pneumonia died, and one child with bronchiolitis subsequently developed spastic quadriplegia; this child had had a convulsion before ventilation was started.

Of 13 patients who primarily had neurological problems, five made a full recovery. Three children with meningococcal meningitis died as did two children with encephalopathy. In one of these the diagnosis remained uncertain, in the other Reye's syndrome was diagnosed. This child was transferred within the first 24 hours to a tertiary referral centre and died two days later. Both children with encephalitis were left with sequelae, one with both physical and intellectual sequelae, the other with just physical sequelae. One child who had a severe head injury became nerve deaf in one ear.

Five cases had had a cardiorespiratory arrest before admission and were resuscitated in casualty; all these children subsequently died: in three of

Table Diagnostic categories of children in intensive care who required respiratory support

Diagnosis	No of children	Mortality	Morbidity
Upper respiratory tract problems (n=14)			
Epiglottitis	8	0	0
Croup	4	0	0
Foreign body	2	0	0
Lower respiratory tract problems (n=18)			
Pneumonia	7	1	0
Bronchiolitis	6	0	1
Asthma	4	0	0
Anaesthetic complication	1	0	0
Neurological problems (n=13)			
Status epilepticus	4	0	0
Meningitis	4	3	0
Encephalitis	2	0	2
Encephalopathy	2	2	0
Trauma	1	0	1
Arrest before admission (n=5)			
Sudden infant death syndrome	2	2	0
Drowning	1	1	0
Infanticide	1	1	0
Congenital heart disease	1	1	0
Miscellaneous (n=4)			
Postoperative ventilation	2	0	0
Chest trauma	1	0	0
Septicaemia, trisomy 21	1	1	0
Total (no (%))	54	12 (22)	4 (9.5)

them intensive support was withdrawn after they were confirmed brain dead, and two had a further cardiac arrest while on ventilation. The diagnoses of this group are given in the table. Of the four children in the miscellaneous group, three made a full recovery. One child with Down's syndrome, a total atrioventricular canal, and septicaemia died.

Seventeen children were admitted to the general intensive care unit who did not require respiratory support. Seven of these children had upper respiratory and two lower respiratory problems, three had neurological problems, two postoperative complications, and three had ingested toxic substances. Of these children, 15 made a full recovery. Two children with severe head injuries were transferred to a neurosurgical centre: one was left with significant neurological deficit, the other died after a period of ventilation in the referral centre.

The mortality of the total 71 patients was 18.3% with a morbidity of 8.4% in the survivors. In the 54 patients requiring respiratory support the mortality was 22.2% with a morbidity of 9.5%. Mortality of

those receiving assisted ventilation on the children's ward was 19% and those on intensive care 24%.

Discussion

There have been no reports of paediatric intensive care from district general hospitals since this department reported its experience in 1970.² In fact, very few other series have been reported recently, although Eastham *et al* described their experience of caring for children on a general intensive care unit in a general hospital that acted as a referral centre for certain paediatric conditions.³ Their overall mortality of 16.6% compared closely with our figure of 18.3%. Comparisons are difficult though in that no two units will accept the same variety of patients. Of the children who died in our series, an appreciable number of deaths (five of 12) were probably unavoidable in that the patients arrived at hospital too late for intensive care to be able to offer them a viable future. Morbidity is the other important measure of success in intensive care. We would accept that our morbidity data may be incomplete in terms of length of follow up in some more recent patients. We could identify only four patients, however, who were left with neurological problems after intensive care and of these three occurred in conditions where sequelae are common even in those not requiring ventilation.^{4,5} Half the combined mortality and morbidity in patients receiving ventilation occurred in those with primarily neurological problems. We do not have the facilities to do intracranial pressure monitoring and we do not have a computed tomographic scanner in this hospital; both of these techniques can be useful in such patients. In each case the difficult decision had to be made as to whether the risks of transporting or transferring the child to a centre that could carry out these measurements justified the potential benefits. Three children were transferred; two died after a period of ventilation in the referral centre and one, who was not ventilated, was left with an appreciable neurological deficit. In those not transferred clinical evidence of raised intracranial pressure was treated empirically with mannitol, dexamethasone, and hyperventilation.

We find there are very few problems associated with caring for children on a general intensive care unit. Almost all the children are cared for in side rooms, which isolates them from the possibly frightening main intensive care area. The environment in the side room can be made more 'paediatric' with the addition of toys, wall posters, a television, etc, as indicated by the awareness of the patient. Initially the nurses in the intensive care unit often feel a certain amount of concern at the prospect of

caring for a seriously ill child. Invariably, at a time when technical skills are most important, they rise to the challenge and most eventually enjoy the experience. When more paediatric input is needed this can be provided by the paediatric department nursing and paramedical staff. There is close co-operation between the intensive care unit and paediatric medical staff; care is taken not to delineate areas of responsibility to the detriment of patient care. The number of medical staff involved in counselling has occasionally led to confusion for the parents, with people saying the same things in different ways and very occasionally saying different things. A uniform approach to counselling parents is of vital importance.

At present there are more problems with providing nursing cover for intensive care on the children's ward. Often it is the senior nurses who have most experience in intensive care, thus a ventilated patient stretches the number of nurses available to run the rest of the ward. Most of the equipment and technical skills used in the care of a child aged less than 1 year are similar to those used in neonatal intensive care. Our department is currently being redeveloped to bring the neonatal unit geographically and administratively onto the same site; this will allow rotation and transfer of nursing staff between the two units, and it will improve development and access to intensive care nursing skills. The experience and technical skills that junior medical staff learn on the neonatal unit transfer easily to the care of these infants. The redevelopment of this department will also include the provision of a purpose built paediatric high dependency area. The current arrangement is to adapt one of the paediatric ward cubicles when the demand for intensive care arises, the main problem with this is the physical difficulty of finding room for all the equipment in the cubicle.

The decision to admit a patient to either area for intensive care is based on flexible criteria. Most of the expertise in ventilation within the paediatric department is with newborn infants. For this reason most of the patients under the age of 1 year are cared for on the children's ward. Older children, who will benefit from the wider experience of the anaesthetic department, will usually be admitted to the general intensive care unit. Other factors, however, will also be taken into consideration—for example, geographical factors. In this hospital the casualty department and intensive care unit are situated close together and are some distance from the children's wards; for this reason an infant resuscitated in casualty may be transferred to intensive care.

It has been advocated that paediatric intensive

care should become more centralised with more children who require intensive support being transferred from district hospitals to central paediatric intensive care units. In this series 61% of patients required respiratory support within four hours of admission most of these in the first hour. Many of those ventilated later than this were due to a sudden deterioration in conditions, such as bronchiolitis, where spontaneous recovery was expected. Thus the experience of the local paediatric and anaesthetic team was crucial in the resuscitation and initiation of intensive care, which is often the most difficult period of intensive care. Centralisation of intensive care will always be necessary for certain types of paediatric illness. Our experience would suggest that total centralisation would dilute peripheral experience and decrease the standards of immediate care these critically ill children would receive and would add to the practical hazards of transporting these children between hospitals.

The results achieved within this unit would support the main recommendation of the British Paediatric Association working party on intensive care that, while each region should have at least one

paediatric intensive care unit, intensive care can and should be done with a wider network of intensive care areas within larger district general hospitals¹

We thank Drs Griffin, Wynne-Williams, Marsh, and Marshall for allowing us to use their patients in this report and for their help with the manuscript. We also thank Mrs Linda Warren and Miss Gail Davies for their care and patience in typing this paper.

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Long term outcome of treatment of end stage renal failure

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SUMMARY The most common causes of end stage renal failure in 46 children (mean age 11 years, range 4-14) treated between January 1972 and June 1977 were: reflux nephropathy (n=12), cystinosis (n=7), focal and segmental glomerulosclerosis (n=6), and Schonlein-Henoch disease (n=5). The quality of life, degree of renal function, and height attainment of the 31 survivors were assessed in June 1985, when their mean age was 22 years (range 14-27), using hospital records and a questionnaire designed to highlight social and psychological problems.

Twenty six patients had a functioning transplanted kidney. Average growth during treatment for all survivors was normal, but most were disappointed with their 'final height'. Though five patients had some form of disabling bone disease, all 31 could walk and 27 could run. Sixteen (67%) were in full or part time employment and nine were living independently.

A group of 32 patients with juvenile onset diabetes treated at this hospital for a least five years were also asked to complete the questionnaire and of these, 17 responded. On average, their data could usefully be compared with those of cases of end stage renal failure. More of the diabetics had jobs, but most sexually mature patients with renal disease were concerned about their physical appearance and had not achieved any stable long term sexual relationships. We suggest that a poor body image resulting in low self esteem may be responsible for the deficiency and believe that further study in this group is warranted.

The first child entered the regular dialysis and transplant programme at Guy's Hospital in September 1968, and the first 10 years' experience of this paediatric programme has been reported.¹ The present study examines the physical state and rehabilitation of those children who entered the programme between 1971 and 1978. These criteria meant that all had received treatment from a coordinated paediatric nephrology service and most had reached adulthood at the time of the study. Though most paediatricians now accept that children with end stage renal failure should be treated, the likely benefits of such lifelong treatment must include the possibility of an enjoyable and satisfying adult life if they are to outweigh the considerable burden of treatment. It was with this consideration in mind, as well as a desire to improve the rehabilitation of our patients, that this study was undertaken.

Patients and methods

Between January 1972 and June 1977 46 children

between the ages of 4 and 14 years were accepted into the regular dialysis and transplant programme at Guy's Hospital. All had had at least one kidney transplanted. Thirty one were known to be alive in June 1985, one had been lost to follow up, and 14 (31%) had died. Degree of renal function of those surviving was obtained from hospital records. The patient's heights were measured by a single observer using the same stadiometer.

The survivors were asked to complete a special questionnaire, designed to obtain factual information on education, employment, marital state, and psychiatric problems, and suspected areas of dissatisfaction within their social and personal lives. The questionnaire (appropriately 'modified') was also sent to 32 patients with diabetes of juvenile onset who had been treated at this hospital for a period spanning their growth into adulthood to provide a useful comparison with the patients with end stage renal failure who also had a chronic and potentially disabling disease requiring lifelong treatment. They differ, however, in that their treatment is less invasive and the risk of premature death lower.

Results

Fourteen patients (31%) died after entering the programme, five in the first year, two in each of the second and third years, one in each of the fourth and fifth years, two in the sixth year, and one in the tenth; 12 of the 14 occurred between 1972 and 1978. The causes of death were known in 10 children: six died from septicaemia, and one each from acute pancreatitis, hyperkalaemia, sarcoma, and encephalopathy associated with cystinosis.

Table 1 shows the primary renal disease of all patients. The unusually large number of patients with cystinosis reflects the unit's role as a supra-regional referral centre. In view of their peculiar growth and metabolic problems patients with cystinosis have been shown separately when their results were significantly different from the other subjects. The 31 survivors had been treated for an average of 10.3 years and had received a total of 48 renal

transplants. Twenty six had stable, functioning grafts (22 with plasma creatinine concentrations of $<150 \mu\text{mol/l}$), four were receiving haemodialysis at home, and one haemodialysis in hospital. Fifteen of the 31 had not had more than 12 months of dialysis.

Twenty nine patients with renal disease and 17 diabetic patients responded to the questionnaire. Table 2 shows the age and sex distribution and duration of treatment. The smaller proportion of diabetic respondents implies an appreciable degree of self selection that might have produced an unrepresentative sample. We were unable to eradicate this problem, resulting in difficulties in interpretation of the data.

GROWTH

Height at the onset of end stage renal failure and at June 1985 (when 27 of the 31 were over 18 years old) was classified according to the number of standard deviations (SD) from the mean of normal children using the Tanner standards for the height of British children.² Girls under 9 years old and boys under 11 were classified as prepubertal; these age divisions correspond to the average age of the onset of puberty in girls and boys, respectively. The mean heights attained are shown in table 3. The changes in mean (SD) height for boys and girls are shown in the figure. The height at the onset of end stage renal failure was not obtained for three boys and three girls.

DISABILITY

Bone disease associated with end stage renal failure or its treatment occurred in five cases (17%). All patients were able to walk unaided, though two were unable to run. None had cystinosis. Seven (23%) had other disabilities or diseases, half of which were known associations of the primary renal disorder—for example, cystinosis and disorders of vision ($n=4$). In the diabetic group 12% had an associated disability.

SOCIAL ACTIVITY, EDUCATION, AND EMPLOYMENT

The special questionnaire provided a simple and subjective assessment of social activities, though the directive format may have encouraged a heightened sensitivity to potential areas of dissatisfaction. Nevertheless, 11 (46%) of the group with end stage renal failure (excluding those with cystinosis) and 10 (59%) of the diabetic patients, said that their social life had been adversely affected by their disease or its treatment. About half of those with end stage renal failure said this problem related to short stature, with obesity and the side effects of drugs playing a part for many. Specifically, 5 (45%) were troubled by driving restrictions, and a similar

Table 1 Primary cause of end stage renal failure in 45 patients*

Diagnosis	No of patients
Reflux nephropathy	12
Cystinosis	7
Focal segmental glomerulosclerosis	6
Schönlein-Henoch disease	5
Familial nephritis	4
Chronic glomerulonephritis	3
Nephropathy	3
Haemolytic-uraemic syndrome	1
Polyarteritis	1
Dysplasia	1
Familial nephritic syndrome	1
Malignant hypertension	1

*In one case no diagnosis was made.

Table 2 Comparison of patients with end stage renal failure and those with juvenile onset diabetes

	EC with end stage renal failure ($n=31$)	No with diabetes ($n=17$)
Sex		
male	11 (45%)	6 (35%)
female	17	11
Average (range) age in June 1985 (years)	22 (14–27)	23 (16–29)
Average (range) duration of disease (years)	13 (8–13)	12 (5–26)
Date of onset of disease	1922–77	1951–80

No significant differences between groups

Table 3 Heights achieved in patients with and without cystinosis

SD score	Boys (n=14)		Girls (n=17)	
	Without cystinosis	With cystinosis	Without cystinosis	With cystinosis
+2 to +3	1	0	0	0
+1 to +2	0	0	0	0
0 to +1	1	0	1	0
-1 to 0	2	0	4	0
-2 to -1	1	0	2 (1)	0
-3 to -2	2 (1)	0	4	0
-4 to -3	3 (1)	2 (2)	2	2 (1)
-5 to -4	2 (1)	0	1	0
-6 to -5	0	0	0	1

All but three boys and one girl had reached final height, figures in parentheses are numbers of boys aged <11 and girls aged <9 at the beginning of the study

proportion felt unable to take part in sports or holiday overseas when they wanted. Among the diabetics, travelling abroad (6, 60%), and attending organised social events (4, 40%), were the major areas of limitation. Four of the five survivors with cystinosis described adverse effects on their social life associated with their short stature and body shape. For them, driving restrictions were usual, though other 'social limitations' were only as common as in other diseases.

Tables 4 and 5 summarise educational achievement and employment records, respectively. In general, those with end stage renal failure compared favourably with the diabetics except that more failed

to attain school qualifications and employment. Only two of the 22 permanent job seekers with end stage renal failure had never had a job, however, and 13 (59%) had kept either one or two jobs for a median of 5.6 years (range 0.5–9.5). Among the job seekers with diabetes, 7 (50%) had held one or two jobs for a median period of 6.0 years (range 0.3–12.0). The subgroup with cystinosis had achieved higher school academic standards than other children with end stage renal failure, although too few (two of five) had completed their education for us to note any effect on employment prospects.

The distribution of socioeconomic class (based on occupation³) was similar between diabetics and those with renal disease: most were in class three. Six (40%) of those with end stage renal failure and 5 (33%) of the diabetics held jobs that were in a lower classification than those of their fathers. Four (26%) diabetic patients had jobs with higher classifications but none of the patients with end stage renal failure had done so.

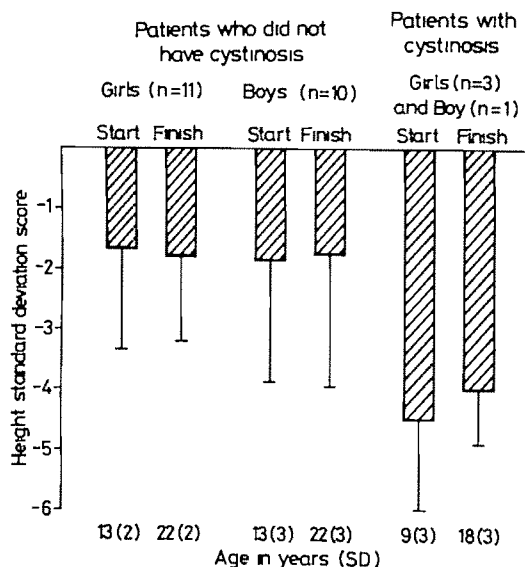


Figure Times of death after entering programme, patients with cystinosis shown separately

ACCOMMODATION AND PERSONAL RELATIONSHIPS

Data from subjects with end stage renal failure due to cystinosis were not significantly different from subjects with other renal diseases on the questions relating to independence from parents, personal relationships, perceived prejudice, and psychiatric disturbance, and the results are not, therefore, presented separately.

Table 6 shows the residential arrangements of patients 18 years or older at the time to the study. A more dominant preference to live with parents or relatives appears to exist in the group with end stage renal failure, but it should be noted that 13 of 17 (76%) of the diabetics were either married (4, 23%) or having long term relationships (9, 53%), but only eight of 27 (28%) of those with end stage renal failure had such relationships.

Table 4 Comparison of educational achievement among groups studied

Highest qualification obtained	Patients with end stage renal failure		
	Cystinosis (n=5) No (%)	Other diseases† (n=21) No (%)	Diabetes (n=17) No (%)
General Certificate of Education			
Advanced level	2 (40)*	2 (10)	4 (24)
Ordinary level	2 (40)*	7 (33)	5 (29)
Certificate of Secondary Education	0	4 (19)	6 (35)
None	1 (20)*	8 (38)	2 (12)*

*One in each group still at school, †three patients did not answer this question

Sexual difficulties were reported by five of the eight patients with renal disease in any form of long term relationship. The remaining 21 interpreted this question as not being applicable to themselves. By comparison, none of the diabetic patients reported sexual difficulties, and two girls each had a child. None of the three female patients with renal failure who had married had had children, though infertility was not perceived as a problem by any patient in either group.

Only four of 24 (17%) of single patients with end stage renal failure over 16 years of age had a stable boyfriend or girlfriend compared with 8 (89%) of single diabetics over the age of 16, even though most considered such a relationship to be desirable.

Half of these in the group with end stage renal failure had not dated a member of the opposite sex in the three months before completing the question-

naire. The feeling of being a victim of prejudice in private and public relationships with others was expressed by 9 (53%) diabetics and 20 (71%) patients with end stage renal failure. Most grievances centred on the areas of job application and opportunity, and to a lesser degree, on obtaining life insurance and achieving satisfactory personal relations (especially with the opposite sex). This last was felt to be linked to poor public understanding of their disease and to the problems of short stature and (in the case of those with end stage renal failure) altered physical appearance.

Seven (41%) of the diabetics and 10 (34%) of those with end stage renal failure had seen a doctor for a persistent emotional or psychiatric problem during the five years preceding the study. Seven (70%) of those with end stage renal failure had seen a psychiatrist, though only one was receiving treatment at the time of the study. No patient had been admitted to hospital for a psychiatric illness.

Table 5 Comparison of No employed in both groups

Type of employment	Patients with end stage renal failure (n=24) No (%)	Diabetes (n=16) No (%)
Full time	14 (58)	13 (81)
Part time	2 (9)	2 (13)
Unemployed	6 (25)	1 (6)
Disabled	2 (8)	0

Table 6 Comparison of types of accommodation between both groups for those aged over 13

Type of accommodation	Patients with end stage renal failure (n=23) No (%)	Diabetes (n=15) No (%)
With parents or relatives	14 (6)	7 (47)
Married, or with others	8 (3)	7 (47)
Alone	1 (4)	1 (6)

Discussion

The overall survival during the period of development of a full paediatric dialysis and transplant service had been disappointing. It should be recognised, however, that the actuarial five year patient survival has improved from 76% between 1968 and 1978 to 90% between 1975 and 1981.⁴ The present data describe a population of survivors of treatment for end stage renal failure in childhood of whom most had renal transplants that were functioning well and in whom physical rehabilitation had been excellent.

Unfortunately, a self selection process among the diabetic patients limited the size of the group for comparison with patients with end stage renal failure and possibly their ability truly to represent the rehabilitation of diabetics as a whole. The diabetic patients had notably better education and employment records than those with end stage renal failure. Using similar criteria to our own, however, a

recent study⁵ of 86 similarly aged diabetic patients treated in another large centre in Britain showed educational and employment performances similar to those attained by our subjects with renal disease. These and other data⁶ suggest that our group of diabetics may indeed be comparatively high achievers. In other areas of this study, however, and in particular those dealing with personal relationships and psychological wellbeing, they are probably more typical of the general diabetic population.⁷⁻⁹ Thus while accepting the limitations of our comparative data, we believe that they suggest several valid conclusions that should be discussed.

The education and employment records of patients with end stage renal failure, though not as good as the comparative group of diabetic subjects, are comparable with those reported in paediatric renal units in other countries.¹⁰⁻¹¹ Nevertheless, the comparison with diabetics showed an association of higher unemployment with lower educational achievement among some patients with renal failure. The obvious conclusion is that the association is one of cause and effect. Clearly the intrusion of repeated hospital admissions and dialyses on a child's education needs to be minimised. Recently this consideration has been emphasised in this unit with the support of an energetic hospital school and its teachers. They provide education and support for children while they are in hospital and form an essential part of the treatment team.

The greatest problem among the subjects with renal disease was that of short stature. Even when patients with cystinosis were excluded from the analysis, 14 of 26 attained a final height greater than 2 SD below the mean. Their final height, however, compares favourably with that of European children treated for end stage renal failure before 1972.¹² Though most of our patients had not grown well before entry to the treatment programme, only a few achieved appreciable catch up growth (including most of the children with cystinosis). Normal growth can be expected for many after transplantation,¹ but other effects of treatment on physical appearance concerned our patients, in particular the development of a cushingoid appearance, obesity, and the ugliness of multiple surgical scars. As expected, patients with cystinosis were the shortest, and nearly all were conscious that their physical appearance was unsatisfactory. Nevertheless, they did not distort the findings for the whole group.

Patients often linked their restricted social life to a preoccupation with physical appearance—that is, short stature and obesity—although to some extent physical disability rather than physical appearance seemed to be the cause (for example, poor eyesight and the resultant inability to drive a motor

vehicle). A study from the United States¹⁰ also reported that poor social adaptation within a restricted social life was common among patients with renal disease. Even more than a restricted social life, we observed a striking failure of our group to achieve lasting relationships as adults with members of the opposite sex. This was a major concern for most patients and contrasted unfavourably with the group of diabetics studied. The high rate of self reported sexual problems in those patients with renal disease who did achieve relationships raised further concern. We suspect that these data (as others have reported) are a reflection of low self esteem due partly to a poor body image.¹⁰⁻¹³ In this context it is important to note that many of our patients received invasive treatment during adolescence, a time when the issues of body image and self esteem are extremely important. We predict that when they become a source of anxious concern the disruption of normal psychosexual development is likely. Certainly our findings are consistent with others¹⁴⁻¹⁶ and affirm the high incidence of psychosexual problems and poor personal relationships in those who have been treated for end stage renal failure during childhood and particularly during adolescence.

Although evidence of the usefulness of psychosocial support and intervention in chronic childhood illness is sparse,¹⁷ and much seems to depend on family composition and personality traits,¹⁵ the results of the present study encourage us to increase the participation of patients and families as partners in the treatment. A higher priority now needs to be given to such measures in the hope that our patients can achieve more complete rehabilitation. To do this we now plan a more detailed study of our subjects using a structured social interview.

We thank the staff of the adult and paediatric renal units, and the diabetic unit at Guy's Hospital for their assistance

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Whooping cough and unrecognised postperinatal mortality

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SUMMARY Trends in postperinatal infant mortality from respiratory causes and the sudden infant death syndrome in England and Wales for 1968 to 1984 were examined. These were compared by time series analysis with changes in the incidence of specific infective diseases and organisms for the same period. Discontinuity was found in association with the occurrence of whooping cough between 1977 and 1982. Associations with the general incidence of respiratory infections and other specific organisms were less evident. An estimate of excess mortality is 460 to 700 deaths, a substantial increase over the certified mortality from whooping cough.

Following concern over the safety of whooping cough vaccine in the middle 1970s, the percentage of children in England and Wales who were fully immunised by the age of 2 years halved. Subsequently epidemics (which occur at about four year intervals) increased in size; fig 1a shows notifications for infants aged 0-1 years.^{1,2} Mortality remained low, only 54 infants having whooping cough as their primary cause of death between 1977 and 1983, compared with 65 in the preceding seven years,³ suggesting that whooping cough was becoming a less serious disease.⁴ Equally likely was that the true mortality from the disease was unrecognised. The mortality is highest among younger patients, in whom the disease can present without the typical whoop or paroxysmal coughing.⁵ In Nottingham during the epidemic 1985-1987 *Bordetella pertussis* caused one near-miss cot death and a fatal respiratory infection in which the diagnosis would easily have been missed from the clinical signs alone. Similar cases have been reported elsewhere.⁶ Both respiratory infection⁵ and sudden infant death syndrome (SIDS) have been certified causes of death in whooping cough fatalities.⁷ Many cases of SIDS have signs of a respiratory illness compatible with early whooping cough.⁸ The terminal apnoea of whooping cough could be indistinguishable from a sudden infant death at home,⁹ but are these covert deaths from whooping cough a measurable cause of infant mortality? If they are we would expect discontinuity in infant mortality to be associated with an increased incidence of whooping cough.

Methods

To look for temporal associations in infant mortality and the incidence of the disease and of other organisms we used time series analysis. By use of different spans and weighting it was possible to investigate long term trends and short term events.¹⁰

CHANGES IN INFANT MORTALITY

Data were obtained from death certificates for infant deaths in England and Wales from 1968 to 1984. The study allowed for two factors that could have influenced the reporting. Firstly, after 1970 infant respiratory deaths were increasingly recorded as being due to SIDS; figures for the diagnoses reflect the trend in reclassification (fig 2). Secondly, the recording of unexpected infant deaths is not standard on death certificates and includes respiratory deaths and asphyxial deaths defined as a death thought to be due to accidental mechanical smothering—for example, in the bed clothes or by inhalation of vomit), as well as SIDS itself.^{8,11} To allow for both factors an estimate of the true trend (fig 2) was derived by adding all the deaths in a particular quarter that were ascribed to respiratory causes (International Classification of Diseases (ICD) codes 460-519), asphyxial causes (ICD codes E911 and E913) and sudden infant death (ICD code 795 until 1978, thereafter code 798). Quarterly rates (referred to as combined mortality) were calculated by dividing these totals by the number of live births in the preceding quarter.

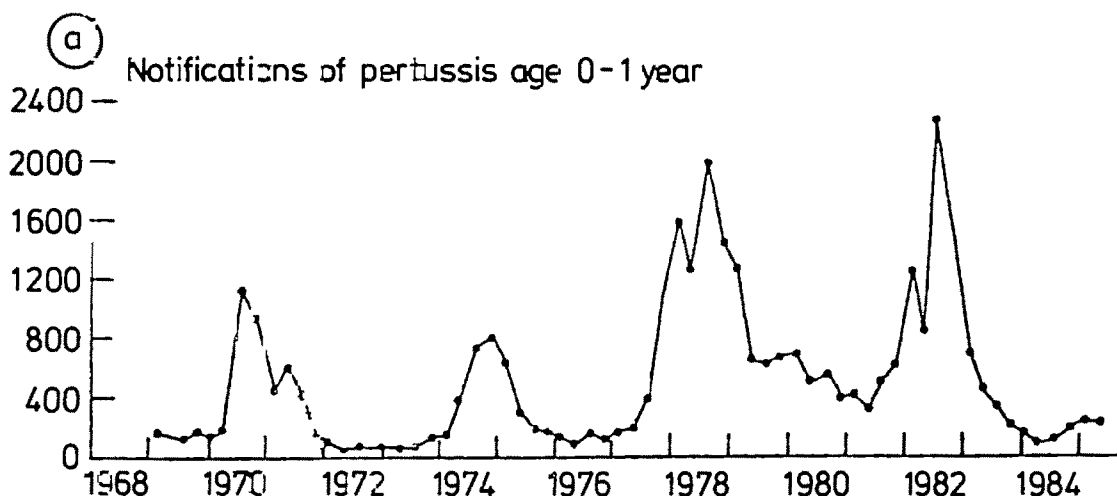


Fig 1a Quarterly pertussis notifications to CPCS for children aged 0-1 years in England and Wales (1968-85).

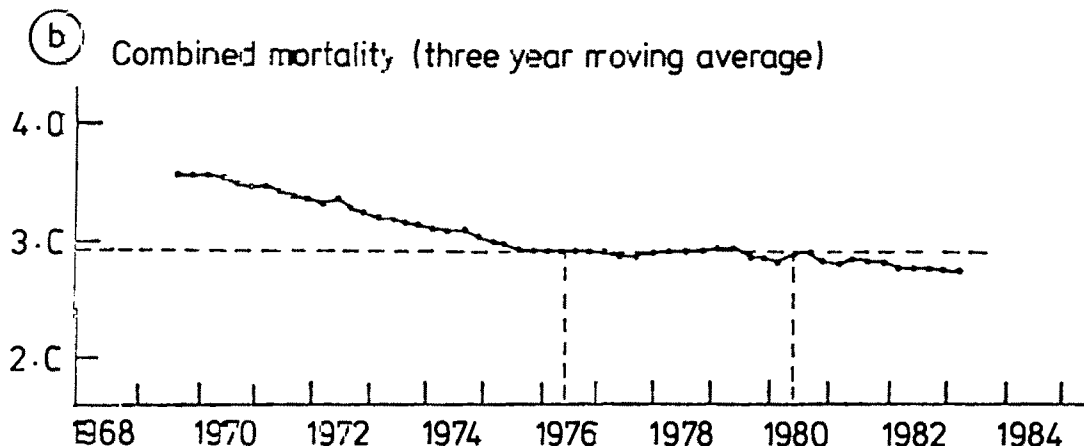


Fig 1b Three year span moving average mortality for combined respiratory, asphyxial, and sudden infant deaths in England and Wales plotted quarterly for the period 1970-85. Dotted vertical lines indicate period decline in mortality halted and resumed

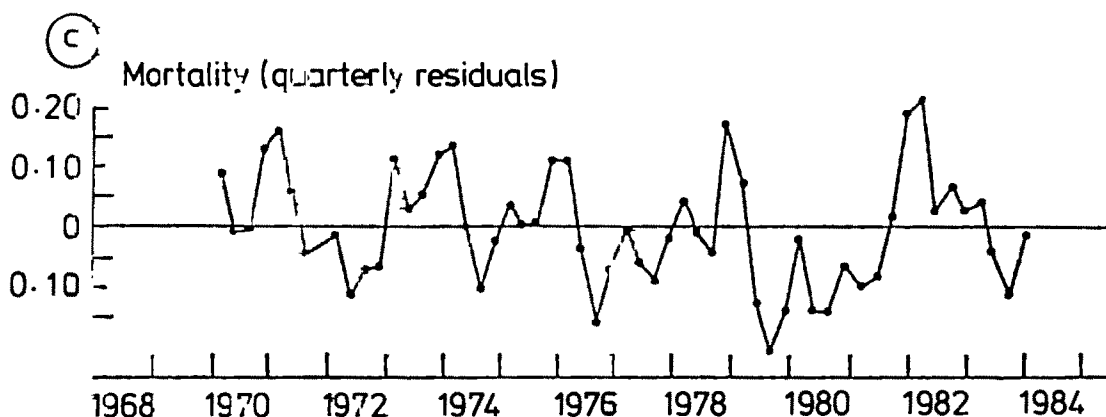


Fig 1c Quarterly residuals of combined mortality (1970-1983)

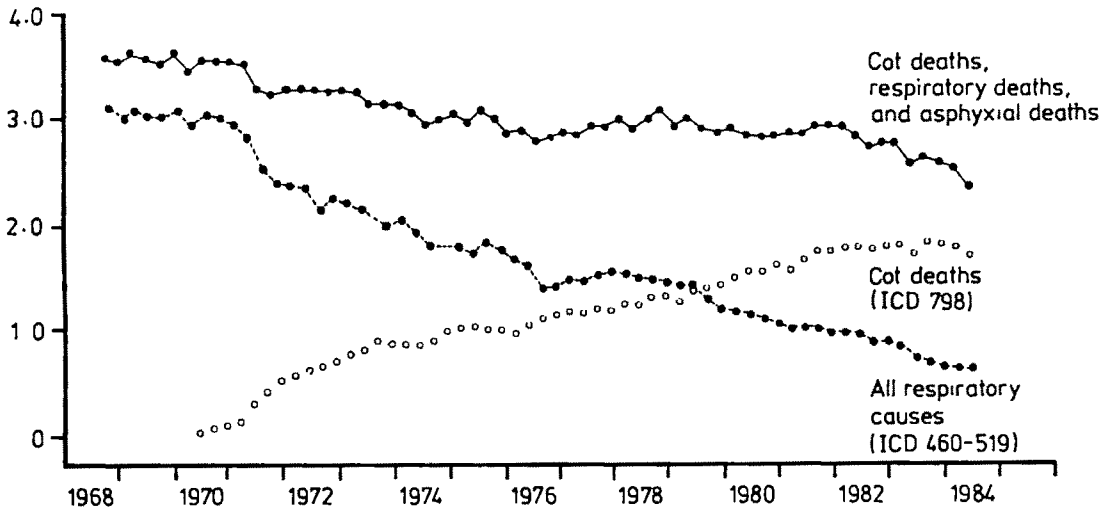


Fig 2 Moving annual mortality plotted quarterly for infant deaths from all respiratory causes, sudden infant deaths, and all respiratory causes, sudden infant deaths plus asphyxial deaths (OPCS data).

This denominator was chosen because 3 months is the peak age of risk for infants dying of respiratory causes and SIDS, and its use is recommended when calculating infant mortality from unexpected death.¹¹ Large seasonal variations in deaths from respiratory causes and SIDS are well known and to look for associations such seasonal swings must be removed.¹¹ This was done by time series analysis using graphs of moving averages—for example, in fig 2 each point represents the mean of four quarterly rates. To see longer term trends a three year rolling average was calculated (fig 1b). Each point was calculated by taking the mean quarterly rate (without weighting) for a three year period plotted at the midpoint. The next point is calculated by moving the three year span forward one quarter, and so on. The same figures for combined mortalities were used to calculate short term events; short term quarterly rates were calculated using a span of nine and peak weighting of 256 by making eight summations in series of adjacent pairs of the original rates.¹⁰ Residuals (fig 1c) were calculated by subtracting each short term rate from the appropriate three year average. A positive residual represents a quarter when combined mortality was above the three year norm, a negative residual the converse. No other time series analysis was performed.

CHANGES IN THE INCIDENCE OF DISEASES AND ORGANISMS

Trends in the incidence of *B pertussis*, other potentially lethal infectious organisms, and respira-

tory disease in general were examined. Data were available from the three sources: disease notifications to the Office of Populations, Censuses and Surveys (OPCS),¹ the Royal College of General Practitioners (RCGP) weekly returns,¹² and organism reports to the Public Health Laboratory Service (PHLS).²

Notifications of whooping cough to the OPCS for children aged 0–1 year were plotted quarterly for the period 1968 to 1985 (fig 1a).¹ All other diseases and organisms were plotted over the same period. Quarterly notifications of whooping cough at all ages from the RCGP, and reports of *B pertussis* from the PHLS were treated similarly (data not shown).

The quarterly incidences of all respiratory diseases with a possible infective cause (common cold, influenza-like illness, sore throat and tonsillitis, laryngitis and tracheitis, epidemic influenza, pneumonia and pneumonitis, acute bronchitis, pleurisy, and asthma) for all ages reported by the RCGP were plotted. These data were only made age specific in 1981, and then only in broad bands—that is, 0–4 years. To remove annual variation these rates were treated in a manner identical with the combined mortalities to show long term (fig 3a) and short term (fig 3b) changes. Quarterly rates for the same disease categories for patients aged 0–4 years were plotted for 1981 onwards but could not be subjected to time series analysis because of the limited period.

Quarterly reports for all ages for infective organisms identified by the PHLS were studied.

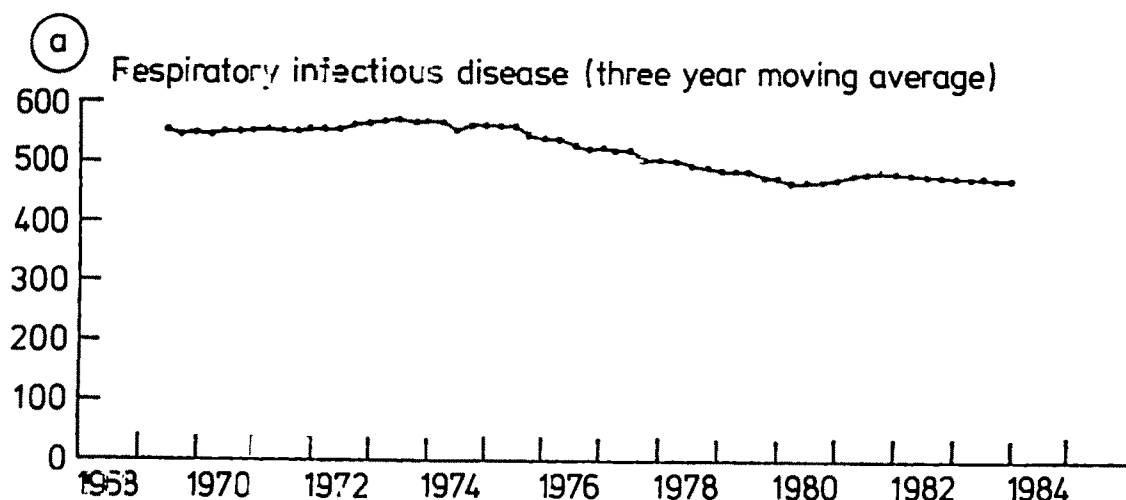


Fig 3a. Three year moving average of incidence of infective respiratory disease for all ages from the RCGP plotted quarterly for the period 1969-84.

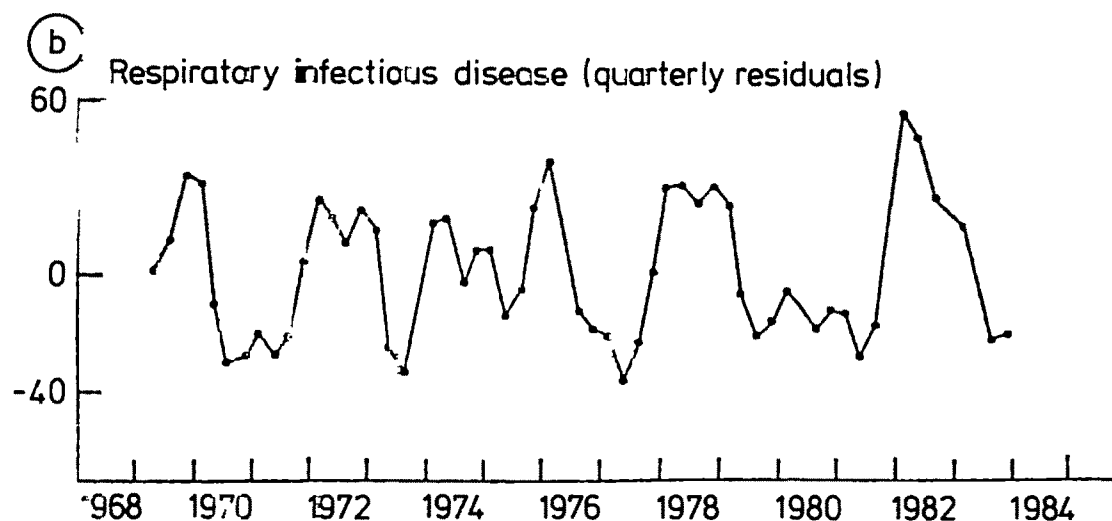


Fig 3b. Quarterly residuals of incidence of infective respiratory disease for all ages from the RCGP (1969-1983).

They were plotted (data not shown) if the organisms had previously been specifically implicated in respiratory or sudden infant deaths—for example, adenoviruses and respiratory syncytial virus, and in one case *Mycoplasma pneumoniae*—and if there was any obvious association with changes in the combined mortality (fig 3c). Finally, the mean quarterly air temperature over the period (compared with the mean for each quarter for the period 1941-1970)² was plotted and subjected to the same long and short term time series analysis (data not shown).

Results

The trends in the notifications of whooping cough (fig 1a) showed not only that there were epidemics in 1977/9 and 1981/2 but that notifications remained high in between—that is, there was an extended epidemic from 1977 to 1982. This was confirmed by the RCGP and PHLS reports. There was a temporal association between long term changes in the combined mortality and the incidence of whooping cough (figs 1a and 1b), though the decline in

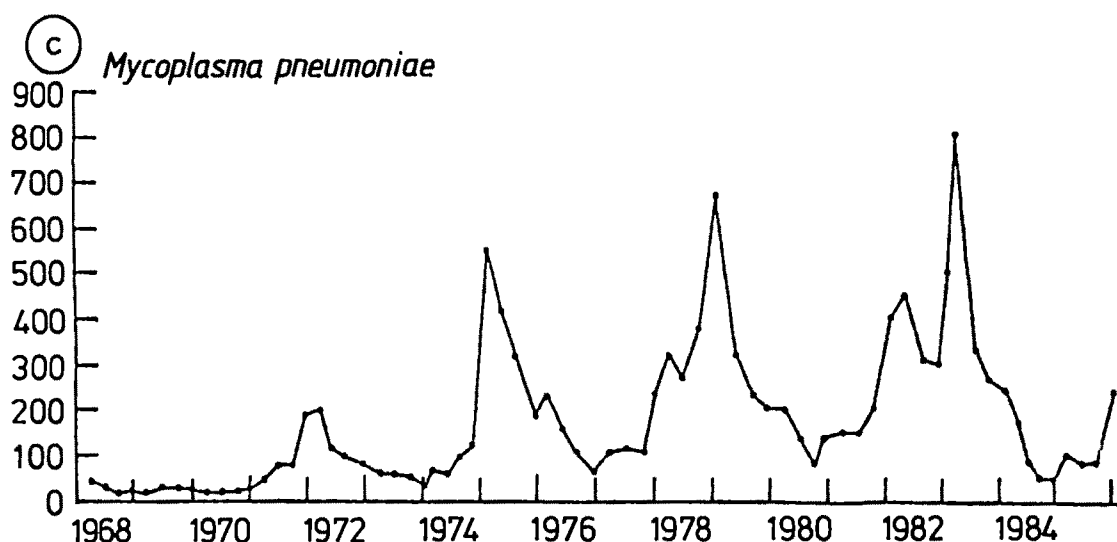


Fig 3c Quarterly identification of *M pneumoniae* by the PHLS (1968–1985)

mortality preceded the end of the extended epidemic. The rate showed a gradual decline from 1968 to 1976 followed by a flattening of the curve until mid 1980; the downward trend then resumed at a reduced rate. The one year moving average (fig 2) showed a similar decline, but with more short term events superimposed. The differences in rates could not be compared directly from fig 1b because consecutive points were not independent, thus a graph of every fourth point of the one year average was considered (not shown). This divided into three clearly defined periods: mid 1969 to mid 1976, mid 1977 to mid 1980, and mid 1981 to mid 1984. The slopes for the three were compared using linear regression analysis. The regression coefficients were: $b = -0.109$, $b = -0.004$, and $b = -0.062$, respectively. The slopes for the first and second periods were significantly different ($p < 0.02$). The differences were not significant when the earlier periods were compared with the third, which may reflect the limited time scale of the latter. Short term mortality after 1976 also had a close temporal correlation with epidemics of whooping cough (figs 1a and 1c), though such events also occurred before 1976.

Due to regular seasonal variations the rates of respiratory illness reported by the RCGP before time series analysis did not show any obvious trends for either all age or 0–4 years plots. The long term trend (fig 3a) showed an overall decline but no association with the flattening of the combined mortality curve, and the quarterly residuals peaked

in association with the epidemics of whooping cough (fig 3b).

With the exception of *M pneumoniae* in the short term (fig 3c), there was no association between organisms reported by the PHLS and the air temperature, and changes in the combined mortality.

A calculation of the excess infant mortality was made from yearly figures using the flattening from mid 1977 to mid 1980 in the graph calculated from the one year average. The population was taken as the live births in the 12 month period starting three months before each year. Two rates of decline were applied: that of mid 1969 to mid 1976 (high excess risk) and that of mid 1981 to mid 1984 (low excess risk). This gave figures (corrected to the nearest 10) of 700 (high excess risk) and 460 (low excess risk). In the same period the number of certified deaths due to whooping cough was 32, giving factor differences of 22 and 14.

Discussion

The discontinuity in long term mortality trends indicates an excess of infant deaths in certain categories during the period 1976 to 1980. We have examined the hypothesis that this was substantially due to undiagnosed whooping cough, and that we may be underestimating its mortality. The long term association between the incidence of whooping cough and the combined mortality supports the hypothesis. (figs 1a and 1b). The early decline of mortality in mid 1980 was explained by the steep

decline in shorter term rates after 1981 (fig 2). There was also a close temporal relation between short term combined mortality and the epidemics of 1977-9 and 1981-3 (figs 1a and 1c). Variations in mortality also occurred, however, before 1976 when epidemics were small and unlikely to make detectable impacts. Hence the previous fluctuations must have been due to unknown factors that may still have been present after 1976. There was also an association between the combined mortality and the fluctuations in the incidence of respiratory diseases in the community (figs 1c and 3a). This finding must be interpreted with caution as the data from the RCGP may not be representative of the community as a whole.¹² If it is true, then either the short term changes in combined mortality resulted from broad fluctuations in the incidence of all respiratory diseases that happened to coincide with epidemics of whooping cough, or the fluctuations in the incidence of respiratory diseases represented covert infection with *B. pertussis* in adults in whom the presentation can be atypical as it can in infants^{5, 12}; as there are no associations between the long term combined mortality and the rates of respiratory diseases (figs 1b and 3a) the latter seems more likely.

Time series analysis is an indirect measure of cause and effect; it can only suggest associations and support hypotheses. It is especially vulnerable to confounding phenomena as it is unable to exclude the possibility of an alternative factor showing a better temporal association.¹⁰ There is also a danger of applying many calculations and selecting those which fit a hypothesis, which is why such manipulations were limited in this study. Is there therefore any further support for the hypothesis? The unusual presentation of whooping cough in the younger patients is additional evidence; this phenomenon has also been reported clinically^{6, 7} and there is a pathophysiological mechanism.⁹ Cherry¹⁴ and Miller *et al.*¹⁵ using indirect methods that were different from ours have shown similar epidemiological patterns and similar excesses in mortality, and in 1931 Stallybrass wrote: 'During the prevalence of whooping cough the rise in the respiratory mortality (bronchitis and pneumonia) under five years of age is often considerably greater than the number of deaths certified as from whooping cough.'¹⁶

The number and type of organisms reported to the PHLS do not reflect the true incidence of disease in the community so we must not dismiss entirely the role of other organisms. Neither can we conclude that such organisms do not cause individual deaths, merely that they do not seem to affect changes in incidence or are too rare to impinge on a population

study. The only organism that showed any association was *M. pneumoniae* and it did not show any short term association before 1976 (figs 1c and 3c), or any long term association. It is also unlikely to cause substantial covert infant mortality; it is uncommon in pre-school children, rarely causes epidemics, and the severity increases with age.¹⁷

We do not wish to imply that whooping cough is the major cause of SIDS. Even if all the excess deaths were due to whooping cough and half appeared as SIDS it could only account for 0.7% to 11% of deaths attributed to SIDS from 1977 to 1980. It is of interest, however, that when notifications of whooping cough finally returned to their usual inter-epidemic low in 1984 (fig 1a), notifications of SIDS also declined (fig 2).¹⁸

The implications of these findings are considerable. Professional and public complacency about whooping cough is one of the factors contributing to poor acceptance of vaccination. The rare dangers associated with immunisation have received a great deal of publicity; a more accurate measurement of the disease's mortality is required so that doctors and nurses can make balanced decisions over the risks and benefits of protecting children.

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Factors associated with maternal choice to provide breast milk for low birthweight infants

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SUMMARY Factors associated with maternal choice to provide milk for premature infants were investigated in 925 mother/infant pairs in five hospitals. A well educated, married, primiparous mother aged 20 or over who delivered a baby boy by caesarean section was nearly 1000 times more likely to choose to express her milk than a mother who was poorly educated, single, multiparous, and aged under 20, delivering a female infant vaginally. Evidence from the five centres suggested that hospital staff have little influence on a mother's choice of feeding method. The major differences between the populations of babies whose mothers do or do not choose to provide milk, raise important issues concerning the interpretation of data from non-randomised clinical trials of feeding premature infants.

The use of human milk for feeding premature infants is controversial, but there is a widely held view that mothers should be encouraged to provide their infants with expressed breast milk as the sole diet or in conjunction with supplementary nutrition. Our multicentre feeding studies have shown that over two thirds of mothers choose to provide their premature babies with breast milk.¹ Data from 925 mother/infant pairs enabled us to find out which factors influence this choice. The subject has already been investigated in mothers of infants born at full term.²⁻⁶ A similar detailed analysis of data from mothers of premature infants ought to answer two important questions: firstly whether health professionals in neonatal units exert a major influence on a mother's feeding preference and hence the availability of preterm human milk in the unit; and secondly, whether there are population differences between mothers who do and do not choose to feed their babies because such information has a bearing on the interpretation of data from the many non-randomised trials that have compared the effects of mothers' milk with another diet.

Subjects and methods

Premature infants weighing less than 1850 g at birth (mean birth weight 1370 g, mean gestation 31

weeks) were entered into a feeding study in five centres between January 1982 and March 1985. Details of the study design have been published elsewhere.⁷ Mothers were free to decide whether to provide breast milk for their infants. A research nurse approached the mother within 48 hours of delivery to enquire if expressed milk was the intended feeding method; by 72 hours all mothers in the study had decided. This analysis is not concerned with how successful mothers were in providing breast milk, simply whether or not they chose to attempt it.

Table 1 shows the associated factors. Social classes were based on the Registrar General's classification, and birth rank was defined as the birth order of living children, the first born child ranking 1, and so on. Twins or triplets in this pregnancy were assigned the same rank.

Smoking history was noted. Data on all the mothers' smoking history were not available for this analysis and are being collected. Problems during pregnancy analysed included toxæmia, infections, surgery, anaemia, threatened abortion, and antepartum haemorrhage.

Although 925 mother/infant pairs were studied, information on social class and mother's education was being collected in a formal interview at the time of writing; data were not available for all patients for the analysis of these two factors.

Table 1 Association between categories and mother's intention to provide breast milk

Category	No (%) of mothers intending to provide breast milk*	p Value
Mother's education:		
University degree or professional qualification	56 (98)	
One or more subjects at GCE advanced level	58 (89)	
One or more subjects at GCE ordinary level or five or more certificates of secondary education (CSE)	187 (75)	<0.0001
One to four CSEs	55 (57)	
No qualifications	144 (54)	
Information not yet available/unclassifiable	191	
Social class:		
1	46 (96)	
2	108 (80)	
3 non-manual	47 (67)	<0.0001
3 manual	207 (65)	
4	65 (68)	
5	14 (40)	
Information not yet available/unclassifiable	224	
Birth rank:		
1	385 (73)	
2	137 (60)	<0.0001
3	56 (56)	
4+	32 (47)	
Parity:		
0	276 (72)	
1	173 (68)	
2	68 (56)	0.0005
3	44 (58)	
4+	47 (53)	
Delivery: caesarean	329 (73)	<0.0001
vaginal	275 (58)	
Parent: married	564 (68)	<0.0001
single	45 (47)	
Mother's age: 20 or over	553 (68)	<0.0001
<20	54 (48)	
Smoking history:		
First trimester—non-smoker	293 (69)	
smoker	179 (60)	0.009
Information not yet available	201	
Second trimester—non-smoker	312 (69)	
smoker	150 (57)	0.0008
Information not yet available	209	
Centre 1	241 (72)	
Other centres	366 (62)	0.002
Toxaemia	145 (72)	
No toxaemia	463 (64)	0.027
Sex of infant: boy	316 (68)	
girl	292 (63)	0.062

*The percentage is based on the numbers of mothers in each category

Statistical analysis was by the χ^2 test, Student's *t* test, or logistic regression as appropriate; linear regression was not used because the dependent variable (choice to provide milk), was categorical.

Results

In an initial analysis of the 925 mother/infant pairs, several factors were examined individually for their association with the mother's wish to provide breast milk or another type of feed. Table 1 shows that a significantly greater proportion of mothers chose to provide their milk if they were better educated ($p<0.0001$), came from a higher social class ($p<0.0001$), had fewer living children ($p<0.0001$) or low parity ($p=0.0005$), were delivered by caesarean section ($p<0.0001$), or had had toxæmia in pregnancy ($p<0.027$). Conversely, fewer mothers chose to express their milk if they were single parents ($p<0.0001$), were aged less than 20 ($p<0.0001$), or if they smoked in the first trimester ($p<0.009$) or—particularly—in the second trimester ($p<0.0008$). There was a strong trend ($p<0.06$) for mothers to provide milk for boys (after adjustment for other factors, this difference reached significance). In one centre (centre 1) a significantly higher proportion of mothers chose to provide breast milk when compared with the other four centres ($p<0.002$). Two further factors that were strongly associated with mother's education and social class, and hence with intention to provide breast milk, were maternal height and head circumference (by Student's *t* test, $p<0.01$); maternal weight was not associated.

Factors not associated with the intention to provide milk were: gestational age, birth weight, multiple births, whether the baby was small for gestational age, whether the mother had been transferred from another hospital (except in centre 1), whether the mother lived outside a 10 mile radius of the neonatal unit, whether the father smoked, or whether the pregnancy was complicated by bleeding, infection, operations, or prolonged rupture of membranes.

Table 2 shows the logistic regression model; intention to provide breast milk was the dependent variable. Only those factors in the model that were significantly associated with the dependent variable are shown; these include maternal education, age, birth rank, marital status, the infant's sex, and the mode of delivery. It should be noted that after inclusion of mother's education or social class in the model the following factors associated with intention to provide milk ceased to reach significance: maternal smoking, toxæmia of pregnancy, inter-centre differences, and maternal anthropometric measurements. In contrast, the association with

Table 2 Odds on choosing to provide breast milk for each significant factor in a logistic regression model

Factor	Regression coefficient	t Value	Odds on electing to provide breast milk
Mother's education:			
University degree or professional qualification	3.53	4.3**	36.3:1
One or more subjects at GCE advanced level	1.65	3.9**	5.2:1
One or more subjects at GCE ordinary level or four or more CSEs	0.79	4.0**	2.2:1
Maternal age (20 or over)	0.84	2.5*	2.3:1
Birth rank 1	0.74	3.9**	2.1:1
Two parent family	0.74	2.3*	2.1:1
Baby boy	0.45	2.5*	1.6:1
Caesarean section	0.46	2.5*	1.6:1
Constant ('worst case')	-1.97		0.14:1

** $p < 0.00$, * $p < 0.02$

having a baby boy increased in significance ($p < 0.02$) after adjustment for other factors. In the 'worst case' for providing breast milk (mother having one to four certificates of secondary education, or no qualifications, age under 20, birth rank over 1, single parenthood, female gender and vaginal delivery of baby) the odds on doing so were 0.14:1 or 1 in 7; the 'best case' odds (mother having a university degree or professional qualifications, and opposites of the above factors) were 128:1.

The constant was set as the 'worst case' for providing breast milk; this was the base line of the model and the odds (0.14:1) are the antilog of the constant. The antilog of individual regression coefficients represent the relative odds of providing breast milk compared with the corresponding worst category—for example, the odds for a baby boy v a baby girl are 1.6:1. The influence of individual factors on the absolute odds of a mother providing breast milk is derived as the antilog of the sum of the constant and the individual regression coefficient(s). In the 'best case' the absolute odds are the antilog of the sum plus the regression coefficients for mothers with higher educational qualifications, aged 20 or more, with a child of birth rank 1, married or cohabiting, with a male child born by caesarean section; these odds are 128:1.

In the analysis each mother/infant pair was weighted equally. Thus the choice made by a mother with twins or triplets was represented more than once—in some instances the choice was different for each baby. A further detailed analysis was undertaken in which each mother (rather than each baby)

was assessed equally. The associations between two factors—the infant's sex or single parenthood, and the intention to provide milk, were found to be stronger in the 68 mothers who had had multiple births than in those who had singleton births; the significance for these two factors was therefore slightly reduced in the weighted model for all subjects. For other factors, associations were the same as in the non-weighted model.

Discussion

There is little information on the factors associated with maternal choice to provide breast milk for premature infants. Maternal feeding preference might be influenced by the special circumstances of premature delivery and by the mother's need to provide milk in an unphysiological manner—that is by manual or mechanical expression of the breast.

For some of the factors analysed our data are similar to those obtained for mothers of infants born at term. Maternal education had a strong influence; an analysis of the raw data showed that 98% of mothers with university degrees or higher professional qualifications chose to provide their milk, compared with 54% of those with no educational qualifications. A similar trend has been described in babies born at term.^{4,8,9} Mothers' feeding preference was better predicted by maternal education than by social class, though social class still showed a strong correlation as in mothers of babies born at term.^{3,4,6}

Some investigators have found that primiparous mothers are more likely to breast feed than multiparous ones^{10,11}, but others have not.^{8,12} In this study, after adjusting for other factors, mothers with a first child were over twice as likely to provide their milk than those with one or more living children. Though this might be associated with family commitments, it has been pointed out that multiparous mothers of infants born at term are influenced by their previous experiences of infant feeding¹³ and so the recent increase in the incidence of breast feeding has meant that primiparous mothers could be expected on statistical grounds to have a higher incidence of breast feeding.

The observed association between maternal age and breast feeding in other studies has depended on the method of analysis. Three group analyses have indicated that it is the oldest and youngest mothers who are least likely to breast feed.^{3,8} In this study we found no less intention to provide milk with advancing age, but in young mothers (under 20 years of age) there was a pronounced reduction in the proportion choosing to do so. Single parents were about half as likely to provide their milk even

after adjustment for age (single parents have a lower mean age than the rest of the population)

Interestingly, mothers were significantly more likely to provide breast milk for boys. This effect was especially noticeable in mothers with multiple births. Most major studies do not report differences between sexes in the incidence of breast feeding following full term delivery.^{3 10} Duration as opposed to incidence of breast feeding has been observed to be greater in girls for certain subgroups of mother/infant pairs,¹⁴ but this may be related to the greater 'demand' for nutrients by boys rather than the mother's attitude to the sex of the child.¹⁵ Sumner and Fritsch¹⁶ suggested that psychosexual factors might influence the mother's attitude towards breast feeding a baby boy; these investigators monitored telephone requests for medical information by new parents in the period immediately after birth and noted that there were twice as many requests for information about the breast feeding of boys than of girls. In another study, however,¹⁷ a similar sex imbalance was found with respect to requested information about bottle feeding, perhaps indicating that there is greater parental concern about boys, though not necessarily implying any sexual connotations. In the present study we did not know what proportion of parents were aware of the poorer clinical outcome of premature baby boys, but such an awareness could have engendered the feeling in the mother that everything possible should be done to help a vulnerable child. The surprisingly high prevalence of mothers choosing to provide breast milk for infants born by complicated delivery (caesarean section) might be explained in similar terms.

Analysis of the raw data (table 1) indicated that cigarette smoking by the mother, especially in the second trimester, gave a negative correlation with the choice to provide breast milk. This effect was no longer significant after adjustment for mother's education but strong trends remained, suggesting that there may be a different attitude to breast feeding among smokers. Guise and Prendergast (unpublished observations) found a significant correlation between smoking and bottle feeding in mothers of babies born at full term, this has also been reported by others.⁵ Paternal smoking behaviour was not found to be significant in this study.

It was interesting that no effect of birth weight or gestational age was found, and even extreme prematurity (47 babies had fused eyelids at birth), seemed to have no influence on the mother's feeding preference. Multiple births, and (with the exception of one centre) transfer to another hospital in the neonatal period, did not seem to deter mothers from choosing to provide breast milk.

It is of clinical relevance to know whether medical staff had any influence on the initial feeding preferences of mothers of premature babies. The five centres in this study (Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield) differed substantially in nature, degree of specialisation in neonatal intensive care, and distribution of social class of the subjects. It is reasonable to suppose that these centres may also have differed in medical staff attitudes to maternal feeding practice. Three centres took a special interest in human milk feeding and had a human milk bank. The intercentre variation, however, that was observed in maternal feeding preferences (table 1) was not seen after adjustment for differences between centres in social class and mother's education. Hospital staff are therefore unlikely to play a major part in influencing a mother's choice to provide milk for her premature infant, though this might not be the case with respect to the 'success' of mothers who do choose to provide their milk; we are currently investigating this hypothesis.

We have shown that the population of infants whose mothers choose to breast feed them differs from the population of infants whose mothers do not. This has important implications for the interpretation of published data from trials of feeding preterm infants and for design of future trials. A non-random comparison of the clinical outcome in infants fed maternal milk and those fed—for instance—on a formula would be misleading in that some major differences in outcome might be associated with group differences in factors such as social class, method of delivery, birth rank, parents' behaviour, and sex distribution rather than with diet alone.

Our findings have shown that a mother's choice to provide breast milk for her premature infant is largely predictable from her education, parity, method of delivery, age, whether she is a single parent or not, and from the sex of the infant. In those mothers for whom all these factors are against providing milk, there is a 1:7 chance of doing so. In contrast, when these factors are in favour, the chances are 128:1; thus in the 'best' case there is nearly a 1000 times greater chance than in the 'worst'.

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Infective endocarditis in neonates

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SUMMARY Five patients with neonatal infective endocarditis were reviewed, two of whom survived. Infection was caused by *Staphylococcus aureus* in four and by *Candida albicans* in one. All cases of bacterial endocarditis had clinical signs of septicaemia, positive blood cultures, thrombocytopenia, microscopic haematuria, and heart murmurs. Three developed skin abscesses early in their illnesses. Three patients had two dimensional echocardiographic studies that showed bacterial vegetations. One of these studies was done before the heart murmur could be heard. We suggest that echocardiography in conjunction with the clinical picture described may help in making an early diagnosis of endocarditis in neonates.

Bacterial endocarditis in neonates is a rare and usually fatal disease; the first survivor was reported in 1983.^{1,2} We became interested in the disease after two patients in our neonatal unit survived. We therefore reviewed all five cases of neonatal infective endocarditis seen at this hospital over the past 10 years to see if we could find similarities that could lead to earlier diagnosis and treatment; this is the largest published series that we know of.

Case reports

CASE 1

A boy weighing 1000 g was born by spontaneous vaginal delivery at 28 weeks' gestation. He required resuscitation after birth with endotracheal ventilation. Sodium bicarbonate and dextrose were given through a catheter in the umbilical vein. His Apgar scores were 1 at one minute and 3 at five minutes. He was transferred to this hospital.

Initial management included mechanical ventilation, intravenous fluid replacement, and treatment with penicillin and gentamicin. Vascular access catheters were inserted in the radial artery and a central vein. At 7 days of age a patent ductus arteriosus was confirmed by two dimensional echocardiography. The heart was structurally normal and the baby was successfully treated with indomethacin.

At 15 days of age he had an abscess over the left posterior iliac spine; a full blood count showed thrombocytopenia and analysis of the urine showed microscopic haematuria. Methicillin resistant *Staphylococcus aureus* was cultured from pus from the abscess, and from the cerebrospinal fluid, blood,

and tracheal aspirates; he was treated with intravenous vancomycin.

At 26 days of age the baby had not improved and a systolic murmur could be heard. Echocardiography showed vegetation round the mitral valve. Despite the addition of fusidic acid to his treatment he continued to deteriorate and died at 28 days.

The diagnosis of vegetative bacterial endocarditis due to methicillin resistant *S aureus* was confirmed at necropsy, together with lung changes consistent with bronchopulmonary dysplasia. There were also periventricular cystic changes and a cerebral haemorrhage.

CASE 2

A girl weighing 2800 g was delivered by elective caesarean section at term. She required resuscitation with endotracheal ventilation. Sodium bicarbonate and dextrose were administered through a catheter in the umbilical vein. Her Apgar scores were 1 at one minute and 9 at five minutes.

She was slow to begin breast feeding and despite the early passage of normal meconium she developed progressive abdominal distension. At 4 days of age she underwent a laparotomy for severe necrotising enterocolitis of the entire colon. Treatment included penicillin, gentamicin, and metronidazole. Vascular access catheters were inserted in the radial artery and a central vein. No organisms were grown from cultures.

A systolic murmur accompanied by congestive cardiac failure was heard postoperatively. An atrio-ventricular canal was diagnosed by two dimensional echocardiography and she was treated with digoxin and diuretics. At 23 days of age, having received no

antibiotics for seven days, she showed clinical signs of septicaemia. *S aureus* was cultured from her blood and she was treated with flucloxacillin and gentamicin. At 25 days of age she developed nodal rhythm and multiple supraventricular and ventricular arrhythmias. She died three days later despite full intensive care.

Necropsy showed vegetations on the pulmonary valve with extension into the main pulmonary artery, which had ruptured. There was an atrio-ventricular canal and patent ductus arteriosus. The bowel showed necrotising enterocolitis and there was an abscess in the loops of small bowel.

CASE 3

A boy weighing 3100 g was born at term by spontaneous vaginal delivery following an uncomplicated pregnancy. His condition at delivery was good. He started breast feeding and was discharged when 5 days old.

At 21 days he developed a fever, a generalised rash, and malaise. Cultures of blood, swabs of the skin lesions, and a specimen of urine aspirated suprapubically grew *S aureus* that was sensitive to gentamicin. A full blood examination showed a platelet count of $10\,000 \times 10^9/l$. Despite initial treatment with penicillin and gentamicin he failed to

respond. At 27 days of age a swab from a skin pustule grew methicillin resistant *S aureus*; treatment with vancomycin and rifampicin was started.

At 28 days a pansystolic murmur was heard and two dimensional echocardiography showed a mobile vegetation attached to the papillary muscle of the mitral valve (fig 1). Fundoscopy showed four choroidretinal atrophic areas and computed tomography of the brain showed several embolic areas.

Antibiotic treatment was continued for six weeks, and echocardiography at 7 weeks of age showed no evidence of vegetations. At discharge he had completely recovered with no obvious sequelae.

CASE 4

A boy weighing 800 g was born at 26 weeks' gestation and transferred to this hospital shortly after delivery. The mother's membranes had been ruptured for four days before delivery and there had been a small antepartum haemorrhage. Apgar scores at birth were 6 at one minute and 9 at five minutes. He was intubated, ventilated at low ventilator settings, and treatment was started with penicillin and gentamicin. Initial cultures showed no evidence of sepsis and his clinical condition was consistent with hyaline membrane disease.

At 2 days of age an echocardiogram was done

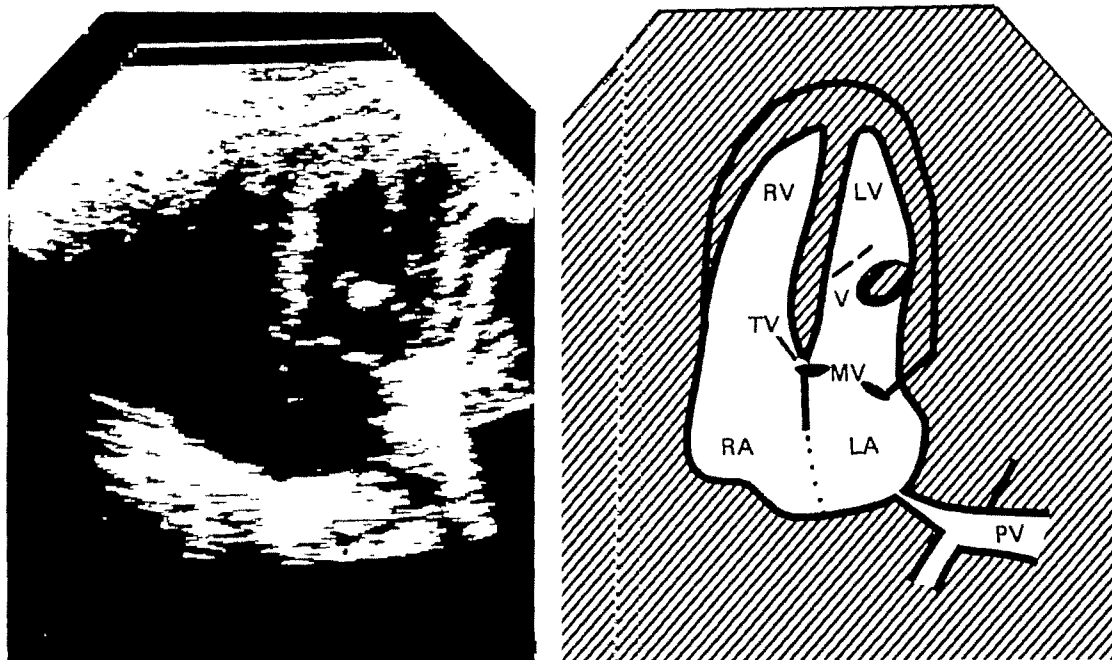


Fig 1 Two dimensional echocardiogram (apical four chamber view) showing pedunculated vegetation in left ventricle attached to papillary muscle. RA=right atrium; RV=right ventricle; TV=tricuspid valve; MV=mitral valve; LV=left ventricle; PV=pulmonary valve, and V=vegetation

which showed normal cardiac anatomy and no evidence of a patent ductus arteriosus. Methicillin resistant *S aureus* was cultured from surface swabs. At 8 days he developed persistent metabolic acidosis and methicillin resistant *S aureus* was isolated from blood cultures; he was treated with vancomycin, but on day 10 methicillin resistant *S aureus* was isolated from a pustule on his chest. At 25 days, nine days after the vancomycin had been stopped, he again developed metabolic acidosis, his white cell count was high, platelets were normal and methicillin resistant *S aureus* was again isolated from blood cultures. Clotting studies were normal and a chest x-ray picture showed bronchopulmonary dysplasia. Treatment with vancomycin and rifampicin was started. A abscess developed on the left wrist and another on the upper arm, and methicillin resistant *S aureus* was isolated from the pus. The cranial ultrasound scan was normal. Two dimensional echocardiography, however, showed a pedunculated vegetation in the left atrial appendage (fig 2). The methicillin resistant *S aureus* isolated from the blood cultures was sensitive to vancomycin, rifampicin, and fusidic acid, but because of possible antagonism between vancomycin and rifampicin, rifampicin was replaced by fusidic acid.

He was extubated at 7 weeks of age at which time he became grossly oedematous with a serum albumin concentration of 19 g/l. This resolved after infusion of albumin and restriction of fluids. Anti-

biotics were continued for seven weeks, at which time cardiac ultrasound scan showed a slight decrease in the size of the vegetation. He was discharged when 12 weeks of age. When reviewed at 12 months of age neurological and developmental examinations yielded normal results. A further echocardiogram showed that the vegetation had disappeared.

CASE 5

A girl weighing 1500 g was delivered at 37 weeks' gestation by caesarean section because of falling oestriol concentrations in the mother's urine; she had had an antepartum haemorrhage at 32 weeks. The infant's Apgar scores were 2 at one minute and 5 at five minutes and she responded to three minutes of endotracheal ventilation. At 24 hours of age she developed tachypnoea and became unwell. Cultures of blood and cerebrospinal fluid grew *S aureus* and she was treated with flucloxacillin and gentamicin. Her condition deteriorated and she developed disseminated intravascular coagulation. An exchange transfusion was carried out but her condition continued to deteriorate and she required mechanical ventilation. She developed severe cholestatic jaundice, and acute hepatic necrosis was suspected. Three further exchange transfusions were carried out; despite full intensive care she died at 19 days of age.

Necropsy showed peritonitis, pleurisy, peri-

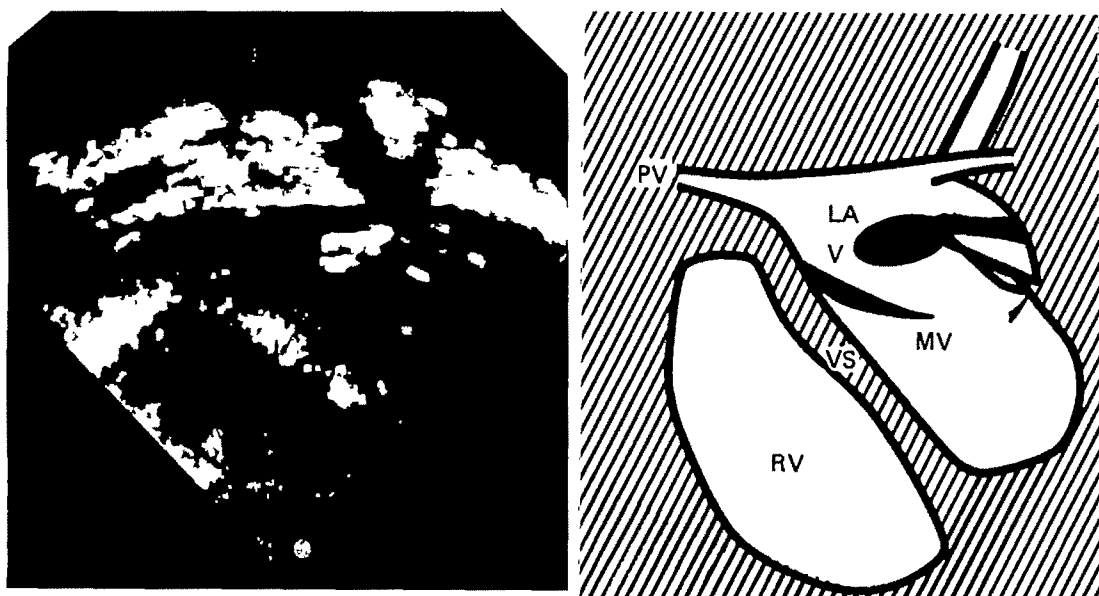


Fig 2 Echocardiogram of a vegetation in left atrial appendage (long axis view) PV=pulmonary valve; LA=left atrium; RV=right ventricle, MV=mitral valve, and V=vegetation

carditis focal necrotic lesions in the spleen, and hepatic necrosis. There was systemic candidiasis with lesions in many organs including the brain. Candida pericarditis and myocarditis were present with a vegetation on the mitral valve that was thought to be the origin of the septic foci in the other organs.

Discussion

The number of reports of infective endocarditis in children have increased during the past 10 years. Symchych *et al*³ reported an incidence of about 3% among 100 neonatal necropsies carried out in one year, but other studies reported lower figures.⁴⁻⁵ The true incidence is difficult to determine.

There seems to be an increased incidence of bacterial endocarditis in children who require resuscitation at birth and subsequent intensive care, especially if central venous lines are inserted.¹⁻⁶ Three of our five cases had had central venous lines in place before the endocarditis developed. All five were clinically unwell and had blood, cerebrospinal fluid, and urine taken for culture before antibiotic treatment was started.

Previous studies have reported that the dermatological lesions of endocarditis such as Janeway's spots, Osler's nodes, and Roth's spots are seen in less than 5% of paediatric patients.¹² In our patients skin abscesses or pustules that were thought to be seedlings of infection from the cardiac vegetations appeared in three of the four patients with bacterial endocarditis. Two of the five developed petechia during their illnesses.

The first echocardiographic diagnosis of bacterial endocarditis was in 1977 by an M mode scan.⁷ In 1983 Kavey *et al* found that 6% of the children with infective endocarditis that they examined had echocardiographic findings compatible with the diagnosis.⁹ Vegetations as small as 1-3 mm could be seen.¹⁰

Murmurs or changing murmurs were present in all four patients later in their illnesses. Thrombocytopenia and microscopic haematuria were present in all babies at an early stage. In two cases the development of a murmur led to two dimensional echocardiographic examination that showed a vegetation. In one case, with the clinical signs of septicæmia, skin pustules, haematuria, and thrombocytopenia, two dimensional echocardiography showed a vegetation in the left atrial appendage before a murmur could be detected. Fourteen days earlier a patient with similar signs was treated with vancomycin for 10 days after methicillin resistant *S aureus* had been isolated from cultures. Echocardi-

graphy at that stage might have shown a vegetation and resulted in a prolonged course of antibiotics with the hope of preventing further damage. Interestingly in older children the mean duration of symptoms before the diagnosis of bacterial endocarditis is 35 days.

With the increasing availability of two dimensional echocardiography neonates with septicaemia, especially if it is prolonged or recurrent, and skin pustules, haematuria, and thrombocytopenia, may warrant a cardiac scan to search for vegetations before a heart murmur has developed.

Non-bacterial endocarditis is an important predisposing factor to the development of bacterial endocarditis because it may form a nidus for bacterial superinfection and increase the possibility of embolisation. In one study of neonates who died 10% had evidence of thrombotic endocarditis at necropsy.³ Eighty per cent of them had had an intracardial central venous catheter inserted. The initial event in the development in thrombi is thought to be endocardial damage, presumably traumatic in these cases.³⁻⁸⁻¹¹ Congenital heart disease is also an important predisposing factor, and it was present in one of our patients. In addition, one report suggested an association between persistent fetal circulation and non-bacterial endocardial thrombosis in neonates.¹²

In bacterial endocarditis the bacteraemia is usually low grade and constant, and detectable in 77-96% of the first blood cultures. This is increased to nearly 100% if three blood cultures are taken.¹³ *S aureus* has become an increasingly common cause of endocarditis since antibiotics have been used, and it is more virulent than other bacterial causes of endocarditis. The complication rate is higher, congestive cardiac failure occurs more often, and mortality increases.¹³ The treatment of infection by methicillin resistant *S aureus* with vancomycin alone is usually satisfactory. There is some evidence, however, that the addition of rifampicin or fusidic acid may improve the response, particularly for endocarditis or when skin infection occurs during treatment. Minimum inhibitory concentrations and minimum bactericidal concentrations of any antibiotic used in the treatment of endocarditis should be routinely tested.¹⁴⁻¹⁵ The serum bactericidal titre should be at least 1/8-1/16, and preferably higher.

Fungal endocarditis in neonates is rare, and we found no other case reports. The diagnosis in our case was made at necropsy, and there was concurrent endocarditis and pericarditis. The occurrence of pericarditis has not been described in neonatal fungal infections, and in neonates with bacterial endocarditis it has only been reported once previously.

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Insulin dependent diabetes in thalassaemia

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SUMMARY Diabetes mellitus was observed in 29 of 448 patients with thalassaemia major attending seven Italian centres. Twelve patients, at onset of clinical diabetes, presented with an asymptomatic glycosuria, 13 with ketosis, and four with ketoacidosis. All were diagnosed after 1979, at a mean age of 17 years. Mean age at diagnosis of diabetes was lower in patients born in the last two decades. In these patients transfusions were started at a younger age and pre-transfusion haemoglobin concentration, serum ferritin concentration, incidence of liver disease, and the presence of a family history of diabetes were higher than in patients born previously. Although 27 (93%) cases had iron chelating treatment the mean serum ferritin concentration was 5600 µg/l. 25 (92%) of these patients had signs of liver impairment. The determination of C peptide in 10 patients showed a wide variation in pancreatic β cell function, and insulin requirements ranged between 0.15 and 1.72 U/kg body weight. Metabolic control was generally poor. The onset of diabetes mellitus was followed in most patients by the appearance of other endocrine or cardiac complications, or both. Fourteen patients died within three years of presenting with overt diabetes. Haemosiderosis, liver infections, and genetic factors seemed to be crucial in diabetes development. Thalassaemic patients developing clinical diabetes mellitus are at high risk for other complications and should be strictly monitored, especially for thyroid impairment.

In recent years there have been many reports of impairment of glucose tolerance in thalassaemic patients who had received frequent transfusions.¹⁻⁵ No detailed descriptions of diabetes in thalassaemia and its complications, however, have been reported. The present study was undertaken to investigate the incidence and clinical and epidemiological characteristics of diabetes developing in thalassaemic patients who had had many blood transfusions.

Patients and methods

The study was carried out of all cases of insulin dependent diabetes mellitus observed in a series of 448 patients with β thalassaemia major who were diagnosed between 1970 and 1983 and followed up at the departments of paediatrics in clinics in Bari, Catania, Ferrara, Genoa, Milan, and Turin in Italy. Standard flow sheets specifically designed to record the history of thalassaemia, any family history of diabetes in first and second grade relatives, the clinical onset of diabetes mellitus and the successive history, and the coexistence of other endocrin-

opathies were used for data collection. Treatment by blood transfusion was the same at all centres.

The concentration of haemoglobin at which transfusions were given was gradually increased from 50-60 g/l in the 1960s to 115-120 g/l in the 1980s according to national protocols.⁶ Desferrioxamine mesylate (Desferal, Ciba Geigy) was given intramuscularly from the early 1970s and by subcutaneous infusion in all patients older than 3 years from 1978-9. Not all patients complied consistently with this treatment.

A diagnosis of diabetes was made on either the classical symptoms or the concentration of fasting plasma glucose being above 7.8 mmol/l on several occasions, or both; this is according to the National Diabetes Data Group criteria.⁷ In each case metabolic control of diabetes was assessed on the personal knowledge of the patient, the concentration of fasting blood glucose, the concentration of glucose in a 24 hour urine sample, and the results of glycosuria monitoring at home. Poor control was arbitrarily defined as the presence of persistent glycosuria or acetonuria or a fasting blood glucose

concentration above 11.1 mmol/l, or both. Urine analysis, liver function tests, thyroid function tests (triiodothyronine (T₃), thyroxine (T₄), thyroid stimulating hormone (TSH) by standard radioimmunoassay techniques), fundoscopy, and electrocardiography were carried out by all the centres at regular intervals. The test for thyrotrophin releasing hormone (TRH) was performed only when there were clinical or laboratory indications. Thyroid function was defined as uncompensated when there were increased TSH and decreased T₄ concentrations or when the concentration of TSH was too low in comparison with that of T₄ or when there was a blunted TSH response to the administration of TRH.

Concentrations of serum ferritin were determined by radioimmunoassay⁸ at a serum dilution of 1:1000 (normal concentrations (SD): men, 108 (68) µg/l, women, 32 (25) µg/l). Residual β cell function was assessed in only 10 patients by C peptide concentrations after stimulation with intravenous arginine: 24 hours after insulin injection arginine hydrochloride (0.5 g/kg body weight, maximum 25g) was injected over 30 minutes, and blood samples were collected at 0, 30, 60, 90, and 120 minutes after the start of the infusion. Percutaneous liver biopsy was performed in 12 patients who had biochemical signs of parenchymal liver damage; informed consent was obtained from parents or patients, or both.

Results

A total of 29 cases (6.5%) of diabetes mellitus (13 male, 16 females) in 448 patients with thalassaemia major, all diagnosed after the tenth year of life, were observed in the seven centres. Altogether 19 cases were observed in Ferrara, five in Milan, two each in Bari and Genoa, and one in Catania; no cases were reported in Turin.

MEDICAL HISTORY UP TO TIME OF DIAGNOSIS OF DIABETES

Mean age at the start of blood transfusion treatment was 13 months for males (range 4–24 months) and 20 months for females (range 3–54 months). In 27 patients (93%) iron chelation treatment was given: they received chelation treatment intra-muscularly for a mean period of six years (range 1–10 years). The details of treatment were available in only six patients: they had a mean dose of desferrioxamine 170 mg/kg/week (range 11–500) and a mean number of doses per year of 154 (range 76–250). Twenty five of the 27 (92%) (of whom 24 were previously treated intramuscularly) received subcutaneous chelation treatment for a mean of 4.9 years (range 1–8 years). Details of treatment were available in

only 17 patients: they had a mean dose of desferrioxamine of 155 mg/kg/week (range 50–280) and a mean number of doses per year of 233 (range 60–340). The serum ferritin concentration at the time of onset of diabetes mellitus was available in 26 patients and ranged from 2300 to 10 600 µg/l (mean 5600). Twenty five of these patients had undergone splenectomy between one and 11 years of age.

Liver impairment was present in 25 of the 27 patients for whom data on liver function were available, and the age when diagnosed ranged from 1 to 21 years, with a mean of 12.6 years in males and 8 years in females. Liver function data in the year preceding onset of diabetes were available in 24 cases and nine had persistently increased serum aspartate transaminase activities. Seven experienced an episode of acute hepatitis during this period. Histological examination of liver parenchyma performed in 13 patients (12 at biopsy and one at postmortem examination) showed siderosis of hepatocytes (grade 1 to 4) in all cases, in addition five had chronic persistent hepatitis, one chronic active hepatitis, and four cirrhosis. No patient had signs or symptoms of heart disease before diagnosis of diabetes.

Oral glucose tolerance was tested in 24 patients before the onset of diabetes mellitus. Impaired glucose tolerance was present in two patients five years before the onset of clinical diabetes, in two patients two years before onset, and in two one year before onset, and in the others a few months before onset. One patient was found to have a condition similar to maturity onset diabetes and remained well controlled for over a year, the only treatment being a restricted carbohydrate diet. A family history in first or second degree relatives with insulin dependent diabetes was present in six patients, seven patients had a relative with type II maturity onset diabetes. Two pairs of siblings with diabetic thalassaemia were reported.

DIABETES MELLITUS

There was a wide range of symptoms at clinical onset of diabetes from asymptomatic glycosuria (12 cases) to ketosis (13 cases), or ketoacidosis (four cases). The mean age at diagnosis was 17 years (range 11–24). There was a progressive decrease of age at onset of diabetes mellitus with the calendar year of birth (figure). While none of the 80 patients born before 1964 developed diabetes before the 15th year (group B, table), nine of the 146 patients born in the following period presented clinical signs between 11 and 14 years (group A). In the younger group (group A) transfusions were started earlier, there were higher concentrations of serum ferritin, a higher incidence of liver disease and acute hepatitis

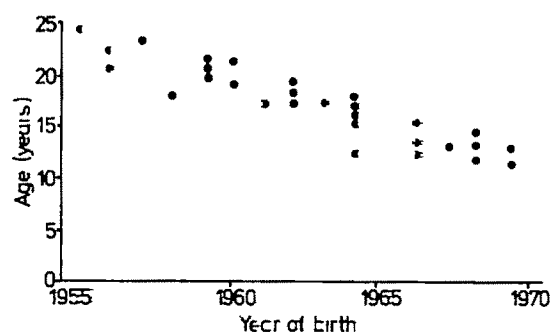


Figure Age at diagnosis of diabetes related to year of birth.

Table Comparison of characteristics at time of diagnosis in patients developing diabetes before the age of 15 years (group A) and after 15 years (group B)

	Group A (n=9)	Group B (n=20)
Males	4	9
Females	5	11
Median age at diagnosis of diabetes (years)	12	18
Range	11-14	15-24
Median age at first blood transfusion (months)	8	21
Range	3-24	6-54
No of patients with pre-transfusional haemoglobin concentrations of over 130 g/l (%)	6 (63)	9 (45)
Theoretical subcutaneous iron chelation* (%)	8 (89)	19 (95)
Median duration (years)	7	5
Range	0-8	0-8
Concentration of ferritin (μ g/l)		
Median	5500	4250
Range	4550-9400	2300-10600
No of patients who underwent splenectomy (%)	7 (78)	18 (90)
No of patients with chronic liver disease (%)	9 (100)	16 (80)
No of patients with acute hepatitis within one year before diagnosis of diabetes (%)	3 (33)	4 (20)
No of patients with a positive family history		
Type I diabetes (%)	3/6 (50)	3/17 (18)
Type II diabetes (%)	3/7 (43)	4/18 (22)

*Compliance with treatment was unknown

in the 12 months before diagnosis of diabetes and a higher incidence of a positive family history.

The mean daily insulin requirement in this series was 0.93 U/kg body weight (range 0.15-1.72). In general terms the metabolic control was good in four patients, poor in eight, and very poor in 17. There was a negative correlation between insulin dose and metabolic control. The determination of C peptide

concentrations in 10 patients from Ferrara showed a variation in pancreatic β cell function: it was increased in one, normal in three, and reduced in six cases. Eleven patients (38%) developed heart disease six to 36 months after the onset of diabetes. In 25 patients the coexistence of other endocrine disease was reported: five had hypoparathyroidism, 19 had hypogonadism, and 14 had hypothyroidism (12 primary and two secondary). No cases of adrenal failure were seen. None of the patients developed clinical complications of diabetes possibly because of the short follow up after diagnosis of diabetes (mean 32 months, range 0-81).

Fourteen patients died within three years of developing overt diabetes. Causes of death were ketacidosis with cardiac failure in one patient, refractory heart failure associated in several cases with severe arrhythmias or cirrhosis, or both in 10 patients, and cerebral thromboembolism in two patients. One patient died at home from unknown causes

Discussion

Glucose intolerance and diabetes mellitus are possible complications in patients with thalassaemia major treated with transfusions.¹⁻⁵ Possible pathogenic conditions are pancreatic cell destruction with consequent insulin deficiency,^{1,2,5} liver derangement with consequent insulin resistance,⁹⁻¹¹ and genetic factors.^{4,5} All these, either singly or together, have been found in our patients with diabetes mellitus. In addition 28% of these patients developed diabetes mellitus shortly after an acute viral hepatitis infection. This suggests that some hepatitis viruses might precipitate diabetes mellitus in thalassaemic patients. No data regarding the clinical picture of diabetes mellitus that complicates thalassaemia major have been reported. We found abnormal glucose tolerance at various stages before the appearance of diabetes mellitus: from five years to only a few months before. A wide range in insulin requirements and a high incidence of poor metabolic control were observed.

During the short period of follow up, disease of the retina, glomerular microvasculopathy, or clinical signs of neuropathy were not observed. Two patients, however, who had undergone splenectomy died one year after the onset of diabetes from cerebral thromboembolism. Rheological factors, due to diabetes, such as enhanced platelet aggregation,¹² increased blood viscosity, red cell rigidity,¹³ and distorted prostaglandin homeostasis^{14,15} might have contributed to the vascular accident in these patients. A high incidence of heart disease of varying clinical severity and a high incidence of

endocrine complications were present in our population. The majority of the 29 diabetic patients with thalassaemia had hypogonadism (19/29) and hypothyroidism (14/29). The precise relation between diabetes mellitus and thyroid disorders is not clear. A possible immunological disturbance was suggested by some authors.¹⁶ In our patients, however, the antithyroglobulin and thyroid microsomal antibodies were not present. Heavy iron deposits have been found in the thyroid gland in patients with thalassaemia, therefore iron toxicity is probably the common factor that causes diabetes mellitus and other endocrinopathies in some patients.

Before the introduction of subcutaneous chelation treatment diabetes mellitus was reported to have occurred at mean age of 17.9 (5.2) years (range 11–25 years).^{1–5} The overall prevalence of overt diabetes in 47 thalassaemic patients older than 11 years was 23.4%.^{1–5} Most of our patients had iron chelation treatment subcutaneously with desferrioxamine on average for 4.9 years. We expected that iron chelation would have been followed by a reduced incidence of diabetes mellitus and an increased age of presentation. In our series we found diabetes mellitus in 29 out of 182 thalassaemic patients (15.9%) who were older than 10 years. Our data show that prevalence is lower in chelated than in unchelated patients, which is what we expected.

Age of presentation, however, has decreased progressively over the years (figure) and instead of being higher was lower in chelated patients. These data seem to suggest that administration of desferrioxamine has precipitated the earlier appearance of diabetes mellitus. This is unlikely, however, as a diabetogenic property of desferrioxamine should also have caused an increased incidence of diabetes mellitus. There must be other causes to explain the earlier appearance of diabetes mellitus in thalassaemic patients who had undergone chelation treatment. The reasons might be: (i) underdiagnosis or undernotification of diabetes mellitus, or both, in the years preceding the subcutaneous administration of desferrioxamine. This seems very unlikely, if not impossible, as it is difficult to believe that diabetes mellitus could remain undiagnosed, (ii) a relative excess of milder cases of thalassaemia in the past years, due to the early death of the patients more severely affected. This hypothesis is very likely and may explain the later presentation of diabetes mellitus in the past; (iii) increased iron load in the younger patients (group A) due to the increased amount of transfused blood not balanced by increased chelating treatment. Before 1980 our patients were transfused when their haemoglobin concentrations were about 95 g/l. Starting from 1980

the transfusion regimen was modified, according to the suggestion of Propper *et al* who proposed transfusion at haemoglobin concentrations of about 115–120 g/l.¹⁷ This regimen was supposed to prevent skeletal abnormalities and hypersplenism without requiring an increased amount of blood, which would worsen the iron overload.

Although our previous evaluations seemed to confirm the Propper data, a recent analysis showed that there is, on the contrary, a direct correlation between pre-transfusional haemoglobin concentrations and blood consumption (unpublished data). This suggests that most of our patients on the regimen maintaining a higher haemoglobin concentration received amounts of blood greater than those transfused in the past and therefore received greater amounts of iron. In addition, the greater number of transfusions increased the risk of viral infections. This might be the cause of the earlier occurrence of diabetes mellitus. On the basis of these observations we do not transfuse until the haemoglobin concentration is lower (about 105 g/l). If we are correct in this policy the incidence of diabetes mellitus in the next few years should be reduced even further and the age of presentation increased.

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Training programme for senior registrars in community paediatrics

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SUMMARY Consultant paediatricians with a special interest in community child health are being appointed in many parts of the United Kingdom but there are few training posts or programmes for this specialty. A training programme for senior registrars in the northern region that three doctors have completed and in which six doctors are currently engaged is presented.

The Court report envisaged an integrated health service for children in which primary care was strengthened and hospital paediatrics were less separate from community paediatrics.¹ It recommended the appointment of consultant community paediatricians, and the need for such appointments is now agreed by the British Medical Association, the British Paediatric Association, and the Central Committee for Community Medicine and Community Health.²

The second Forfar Report highlighted the fact that many senior medical staff in community child health were not adequately trained or qualified.³ It described how suitably trained senior clinical medical officers might become consultant paediatricians with a special interest in community child health and proposed that junior staff should train to become consultant paediatricians in this specialty. Recently the specialist advisory committee (SAC) in paediatrics of the joint committee on higher medical training has drawn up an outline senior registrar training programme (Professor I B Houston, personal communication). Many health authorities are now appointing specialist consultants, but the realisation of their importance has come before many training posts have been created.

In 1982 the need to appoint to consultant posts in community paediatrics only those whose training was appropriate led to discussions between district medical officers, specialists in community medicine, and consultant paediatricians of the Newcastle, Northumberland, and North Tyneside health districts and the Departments of Child Health and Family and Community Medicine of the University of Newcastle upon Tyne. These resulted in a programme of higher professional training in community paediatrics that three doctors have now completed and in which six are currently engaged.

Description of the training programme

To be considered for the training programme applicants must have completed general professional training with at least three years postgraduate experience in hospital and community paediatrics and must usually hold the MRCP diploma. The training programme lasts four years; although some trainees whose previous experience is appropriate may require less, all are committed to at least two years of the programme. Four of the posts are funded by health districts that converted vacant clinical or senior clinical medical officer posts into training posts. The upper end of the clinical medical officer pay scale in fact corresponds to that of the senior registrar. Some trainees do on call work to match the extra salary a hospital senior registrar receives for this work. The other two posts are funded directly by the Department of Health and Social Security (DHSS) scheme for doctors with domestic commitments who wish to train part time.

COMPONENTS OF THE TRAINING PROGRAMME

Specialised training modules

Each module is supervised by a consultant in that

Table *Specialised training modules and their duration*

Child psychiatry	Full time	6 Months
Mental handicap	2-3 Days per week	6 Months
Child development centre	2-3 Days per week	6 Months
Orthopaedics	2 Days per week	4 Months
Ophthalmology	2 Days per week	4 Months
Otology	2 Days per week	4 Months
Paediatric neurology	1-2 Days per week	6 Months
Epidemiology and statistics	20 Sessions	

specialty. The table shows the modules and how long they take. Those modules in child psychiatry, mental handicap, and assessment of handicapped children require the trainee to carry direct clinical responsibility for patients as a member of a consultant led team. Those in orthopaedics, ophthalmology, and otology give the trainee opportunities to observe children in clinics, to visit schools, to work with paramedical staff, and to study the conduct of screening programmes connected with those specialties. Training in epidemiology is provided through modules for trainees in community medicine.

Research

Each trainee must develop a major research project, which is usually supervised by a member of the university. Examples of projects so far include studies of bereavement reactions in children, infant colic, circumstances surrounding childhood deaths from asthma, impedance and orthoptic screening in preschool children, and the development of a preschool health surveillance programme.

Organisational and clinical work in a health district

The trainee learns about services for children and the care of children in the community by having responsibilities within one health district. These vary between health districts and examples are listed as follows.

- (i) Leading a team of clinical medical officer, senior house officer, school nurse etc, who are responsible for a geographically defined area within a district.
- (ii) Membership of a district handicap team or equivalent
- (iii) Clinical responsibility for a group of children with special problems—for example, the partially hearing.
- (iv) Membership of committees such as the Pre-School Playgroup Association, Home Start, Health Education, education, adoption, and fostering.
- (v) Responsibilities for child abuse, supervised clinically by the specialist consultant paediatrician, and administratively responsible to the Area Review Committee.
- (vi) The setting up of training programmes in health surveillance for family doctors and health visitors.

It is expected that some of these responsibilities will be carried throughout the four years of the training, while others will be assumed as time allows. The clinical work is supervised by a consultant community paediatrician if there is one in post or by a consultant paediatrician in conjunction with the specialist in community medicine (child health).

The organisational work is supervised by a consultant community paediatrician, a specialist in community medicine, or a district medical officer as appropriate.

Hospital paediatric work

A consultant community paediatrician will often have responsibilities in hospital; he or she may see new outpatients and refer some children from the community to hospital for investigation. Therefore, continuity and integration of care should be taught at senior registrar level. Currently half the trainees conduct a regular hospital outpatient clinic and may admit patients to hospital under the overall care of their supervising consultants. The others do not conduct a hospital clinic at present but it is clearly desirable that they do. Whether the trainee joins an on call rota will depend on the needs and previous experience of the individual. On completion of training all trainees must have had sufficient experience in acute paediatrics to be able to join a consultant on call rota if necessary.

Discussion

New ideas for improving the services and the care that children receive have created the need for training initiatives. One way of providing senior registrar training in community paediatrics is to incorporate a year of community experience into an existing hospital rotation. The alternative is to design a new post and programme. We favour the latter approach because we think that neither the necessary breadth and depth of experience nor the appropriate orientation to the work of community paediatrics can be provided in a single year away from hospital. To set up a new post there needs to be careful planning by paediatricians and community physicians and a willingness by health authorities to direct funds to this training. Conversion of a clinical or senior clinical medical officer post to a training post reduces the 'service' component. As already mentioned, however, the need for training results from the recognition of the need for new approaches to the delivery of the service. Therefore, time might occasionally be released by a development in the service—for example, by changing the emphasis placed on routine medical inspections in school. As well as a long term benefit, there is also an immediate benefit to the health districts that set up training posts, as these attract doctors of high quality, experience, and commitment.

Training for community paediatrics cannot develop in isolation and for training to be well received by health authorities, prove sustainable in terms of consultant supervision, and be valuable to the trainees certain criteria are necessary.

EFFECTIVE ADMINISTRATION

A training committee should oversee the training programme. In our region, this is the Education Committee for Community Paediatrics of the Postgraduate Institute, with representatives from all health districts in the northern region, the university, and paediatrics. This committee also oversees the training of senior house officers in community paediatrics and clinical medical officers. Senior registrar training is thus part of an overall strategy for training in community paediatrics in the region.

EFFECTIVE SUPERVISION

This is required at many levels. Firstly, the SAC should inspect the posts, advise on improvements, and determine whether they meet national requirements. When our programme began the SAC could inspect only senior registrar posts. The regional registrar and senior registrar committee therefore granted honorary senior registrar status to our posts. We welcome the fact that the SAC will now also inspect senior clinical medical officer posts designated for training. Secondly, the regional education committee should interview trainees annually to discuss individual problems and progress. Thirdly, each trainee should have named supervisors for the clinical, organisational, and research parts of the training. The importance of effective supervision was well expressed by the SAC 'It is important to appreciate that one of the basic differences between simply doing a job of work and receiving an education in it is the quality and quantity of discussion, advice, supervision and stimulation provided by the supervisors.' Fourthly, the senior registrars should themselves supervise or instruct others such as senior house officers, nurses, or paramedical staff in community paediatrics.

COLLABORATION WITH SPECIALIST SUPERVISORS

Organisers of the programme should listen to the comments of the consultant supervisors in the specialist modules on the progress of the programme and its relevance to that specialty. For example, the trainer in paediatric neurology found the module to be unsatisfactory because of conflicts between the complexity of the tertiary referral service and the trainee's need for clinical responsibility. This module needs to be redesigned.

THE INFORMAL CURRICULUM

Occasional meetings of the trainees, usually in the evening at one of their houses, enabled them to compare their experiences, discuss their training, and to arrange special tutorials by invited teachers—for example, on the subject of child abuse. Their discussions about training have helped to shape its format, ensure that, overall, it has been enjoyed

and identify weaknesses. One trainee thought that more time should be devoted to formal training in communication skills. Another trainee thought that the training did not sufficiently emphasise a sociological view of health nor the importance of community work in improving child health. Another trainee thought that her organisational and clinical work in a health district was not properly supervised.

The training programme emphasises core components that every trainee must complete. This both sets a standard and imposes an obligation on health authorities to ensure that sufficient time and money are available for these. The programme, however, does not specify every topic that could be included in community paediatric training. The senior registrars are already experienced paediatricians and must have time to develop their own special interests in depth.

As the importance of the role of the consultant community paediatrician is recognised and authorities attempt to implement the recommendation that there should be at least one consultant in this branch of paediatrics in each district, there will inevitably be a shortage of those whose training has specifically prepared them for such a post. Under these circumstances authorities may be tempted to appoint candidates whose training or experiences is less than adequate. We believe this would be misguided, for the quality of service at secondary care level in the community envisaged by the Court report can only be achieved if the consultant community paediatrician is both perceived by others and him or herself to be a paediatrician whose training has fully prepared him or her for that role. Such training must now be seen as an urgent national priority.

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Short reports

Total parenteral nutrition and sepsis

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SUMMARY In 1279 very premature or very low birthweight infants the use and duration of treatment with total parenteral nutrition were associated with short gestational age and low birth weight. Infants treated with total parenteral nutrition had a higher risk of sepsis usually caused by *Staphylococcus epidermidis* or *Staphylococcus aureus*.

In very low birthweight (VLBW) infants sepsis is a major problem and an important cause of mortality. Recently changes in incidence and causative organisms have been reported^{1,2} duplicating hospital acquired organisms, particularly *Staphylococcus epidermidis* and *Staphylococcus aureus*.^{1,3} These organisms are often isolated from children who have long term indwelling intravenous catheters in situ.^{1,4}

Few reports have focused on very low birthweight infants. We therefore used the Project on Preterm and Small for Gestational Age Infants to collect prospective data on 1258 infants born alive in 1983 with a gestational age of less than 32 weeks or a birth weight of less than 1500 g, or both.⁵ We studied the use and duration of total parenteral nutrition, the incidence and nature of the sepsis, and the association between them.

Patients and methods

Data on total parenteral nutrition (defined as the infusion of glucose, amino acids, and fat solution intravenously for more than 24 hours) were available for 1279 infants; the remaining infants had died shortly after birth.

Firstly, we investigated the use and duration of total parenteral nutrition, the incidence of bacteriologically confirmed sepsis (defined as a positive blood culture and identification of the causative organism) and clinical sepsis (clinical symptoms and haematological changes such as leucocytosis, neutropenia, an increased number of band cells, or thrombocytopenia) and the association among these

factors, using the non-parametric Kruskal-Wallis analysis of variance. Secondly, we analysed the association between total parenteral nutrition and sepsis using logistic regression analysis. Total parenteral nutrition was entered into the logistic regression equation as an input variable, sepsis as an outcome variable, and gestational age and birth weight as potential confounding factors. The odds ratio was calculated as a measure, comparing the risk of developing sepsis when the infants were or were not treated with total parenteral nutrition.

Results

A total of 822 infants (64%) were treated with total parenteral nutrition. The incidence of treatment was highest (over 80%) in infants with birth weights below 1000 g and gestational ages of 28-32 weeks. More than half the infants were treated for longer than a week, 53 infants for more than four weeks (table 1). The duration of total parenteral nutrition was positively and significantly associated with a lower mean gestational age ($p < 0.0005$) and lower mean birth weight ($p < 0.0001$).

Clinical sepsis was present in 486 cases (38.0%), and bacteriologically confirmed sepsis in 138 (10.8%). Both were clearly associated with the duration of total parenteral nutrition (table 1). No association

Table 1 Duration of total parenteral nutrition, clinical sepsis, and bacteriologically confirmed sepsis

Duration of total parenteral nutrition (days)	No of infants (%)	No with clinical sepsis (%)	No with bacteriologically confirmed sepsis (%)
0	457 (36)	99 (20)	28 (20)
1-7	396 (31)	126 (26)	33 (24)
8-28	373 (29)	222 (46)	65 (47)
>28	53 (4)	39 (8)	12 (9)
Total	1279 (100)	486 (38)	138 (11)

Table 2 Causative organisms in bacteriologically confirmed sepsis

Organism	Patients not receiving total parenteral nutrition No (%)	Patients receiving total parenteral nutrition No (%)
<i>S. epidermidis</i>	1 (4)	40 (36)
<i>S. aureus</i>	3 (11)	21 (19)
<i>E. coli</i>	7 (25)	17 (16)
Streptococcus group B	8 (29)	10 (9)
Other	9 (32)	22 (20)
Total	28 (100)	110 (100)

was found between sepsis and gestational age or birth weight.

Logistic regression analysis with total parenteral nutrition as an input variable, clinical sepsis as an outcome variable, and gestational age and birth weight as potential confounding factors, showed that infants treated with total parenteral nutrition had a significantly higher risk of sepsis (odds ratio 3.1; 95% confidence interval 2.4 to 4.0; $p < 0.0001$) than infants not so treated. Total parenteral nutrition for more than seven days was even more strongly associated with sepsis (odds ratio 4.4; 95% confidence interval 3.4 to 5.6; $p < 0.0001$), compared with those who had received it for seven days or less, or those who had not received it at all.

The bacteria isolated from the blood cultures in cases of bacteriologically confirmed sepsis in treated infants showed a pattern different from that in infants not given total parenteral nutrition; with *S. epidermidis* and *S. aureus* outnumbering other micro-organisms (table 2).

Discussion

Between 1977 and 1978 La Gamma *et al* found that 48% of infants with birth weights below 1000 g received partial and 37% received total parenteral nutrition.⁶

In our study population 64% of infants were treated with total parenteral nutrition, a doubling of its use over five years. The widespread use of this kind of intensive treatment reflects the fact that the commercially available solutions have been adapted for premature newborn infants.

The association between indwelling catheters and the occurrence of sepsis, described in reports on smaller study populations, was confirmed in our large survey.^{1,6} The association between the use of total parenteral nutrition and sepsis was clear, as was the association between the duration of total

parenteral nutrition and sepsis. The amount of perinatal data available enabled us to take the most important potential confounding factors into consideration when we further analysed this association by a multivariate statistical technique. Low gestational age might have been in itself associated with sepsis, and because its association with the duration of total parenteral nutrition is clear it might have caused the 'crude' differences we found. By including gestational age in the logistic regression analysis, the calculated odds ratio (3.1) is corrected for gestational age; that means that the increased risk of sepsis is associated with total parenteral nutrition.

As far as causative organisms are concerned, *S. epidermidis* and *S. aureus* were found in 47% (65 of 138) of all cases of bacteriologically confirmed sepsis, which is in keeping with the findings in a smaller study group.⁶ In our infants treated with total parenteral nutrition this was the case in 55% (61 of 110), increasing from 46% of infants given total parenteral nutrition for less than a week to 84% of infants treated for more than four weeks. Sepsis in infants not so treated was more often caused by *E. coli* and streptococcus group B.

The present study has shown that the use of total parenteral nutrition is widespread in The Netherlands. Although the risk of sepsis seemed to be significantly increased by total parenteral nutrition, the causative organisms were fairly benign. We suggest that the advantages of total parenteral nutrition outweigh the disadvantages of sepsis in this group of infants.

We thank the 101 paediatric departments in The Netherlands that participated in the collaborative Project on Preterm and Small for gestational age Infants, for supplying the data, and the Praeventiefonds, The Hague (grant 28-766) for financial support.

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Spastic hemiparesis and presumed prenatal embolisation

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SUMMARY An infant with clinical evidence of prenatal right subclavian arterial occlusion subsequently developed left hemiparesis with cystic infarction of the territory of the right middle cerebral artery. Perinatal strokes have not been reported with signs of limb ischaemia at birth; this finding may be a warning of possible simultaneous cerebral infarction.

Embolic² and thrombotic³ events, as well as primary haemorrhagic lesions in association with congenital vascular malformations or tumours¹ cause strokes or cerebral infarction in neonates and the fetus.² Strokes occurring early in fetal life result in cortical neuronal loss and architectural changes ranging from hydranencephaly to porencephaly⁴; if they occur later in gestation or in infants born at term, they are characterized by cystic changes similar to those found after cerebral infarction in adults. Infarction due to thromboembolic disease may not be limited to the brain; other organs or parts may be obstructed simultaneously.¹ The detection of external vascular obstruction such as peripheral cyanosis and an absent pulse in a limb should therefore raise the possibility that a vascular occlusion of a more vital part (such as the brain) had occurred at the same time.

We report an infant who presented with short lived cyanosis of the fingers and an absent pulse in the right upper limb; these were the only abnormal findings in the neonatal period but she was subsequently discovered to have had an infarct of the ipsilateral part of her brain.

Case report

A baby Asian girl was born in Scotland at term following an uneventful pregnancy and labour. The placenta was described as incomplete with ragged membranes. The antenatal history was unremarkable.

The infant's birth weight was 2760 g, length 55.5 cm, and head circumference 33.5 cm. Apgar scores were 9 and 10 at one and five minutes, respectively. Cyanosis of the right fingers and limitation of movement of the right upper limb were noted. No pulses were palpable in the right upper

limb but elsewhere they were normal. The arm and forearm circumferences, measured at midpoints, were 1.0 cm smaller on the right than on the left. The rest of the physical examination was unremarkable.

Pain radiographs of the cervical spine, chest, and right shoulder were normal. A full blood count on day 1 yielded the following results: haemoglobin concentration 223 g/l; packed cell volume 63%; white cell count $20.2 \times 10^9/l$ and platelet count $80 \times 10^9/l$. Viral studies were all negative. A splint was applied to the affected limb.

On the second day of life the tip of the right ring finger had become dark blue, though the other fingers were viable. Doppler ultrasound scan of the affected limb detected pulsation in the right subclavian artery to the outer border of the first rib, but not beyond. Over the next 72 hours the Doppler pulsation became audible in the axillary artery down to the radial artery and pulses could be felt. The infant remained otherwise well.

On discharge at the age of 2 weeks movements in the affected limb had considerably improved and all the pulses were palpable. The range of active movements of the left limbs were within normal limits. Because the improvement was so rapid no further investigations were carried out. The child subsequently failed to attend the follow up clinic.

At the age of 7 months the infant was brought back to the clinic the mother complaining that since the age of 4 months the child had had limited use of her left limbs; she had otherwise been well. A full neurological examination showed a left spastic hemiparesis and left hemianopia. The head circumference had dropped to the 10th centile having been on the 25th centile at birth. Her right upper limb was normal, as was her social behaviour. Computed tomography brain scan at the age of 7 months showed a cystic lesion in the area of the right middle cerebral artery with shrinkage of the right hemisphere (figure). When reviewed at 17 months of age, she could only move about by shuffling on her bottom but she appeared cognitively normal and no seizures had been observed.

Discussion

The presence of muscle wasting in the ischaemic



Figure Computed tomogram at 7 months old showing large cystic structure (presumed infarct) in area of right middle cerebral artery.

limb at birth strongly suggested a prenatal vascular occlusion. Although signs of cerebral impairment were not detectable during the neonatal period, we assume that the two ischaemic events occurred simultaneously in utero, as the presumed obstruction occurred in vessels derived from a common trunk—the innominate artery—through which the emboli could have passed. Apart from the limb ischaemia, the absence of signs of an acute illness after birth rule out the possibility of an intracranial event occurring postnatally.

It is known that cerebral infarcts occur in the fetus and in neonates.^{1,5} Cyanotic congenital heart disease,^{1,5} the placenta, and choriohaemangiomas have been suspected as sources of emboli. Factors which encourage formation of thrombi include asphyxia with hypotension, polycythaemia,³ and intravascular coagulopathy due to infection.¹

A case of prenatal stroke has been described in association with haemolytic anaemia of the fetus caused by Rhesus incompatibility.² In none of the three cases of prenatal infarcts described by Ment *et al* could the cause be explained.⁵ In our patient there were no maternal or fetal factors to establish the cause or the origin of the thrombi or emboli. Perhaps the placenta, which was described as

incomplete with a ragged membrane, could have trapped platelets as the infant's count was low.

Rapid lysis of thromboemboli occurs in neonates because of high concentrations of circulating fibrinolysins,⁶ which may explain why the pulse in the limb was established within 72 hours of birth.

Neonates with cerebrovascular accidents usually present with lethargy, hypotonia, cardiopulmonary failure, and death. Survivors go on to develop hemiplegia, epilepsy, and mental handicap.^{1,5} The degree of morbidity seems to be associated with the predisposing disease and not with the cerebral infarct per se.¹ In addition, the age at which symptoms appear varies. Most infants become symptomatic on the first day and die within the first month,^{1,5} but a few present later. One infant born at term in the series described by Ment *et al* developed poor vision and spastic quadriplegia at 9 weeks of age.⁵ Before that the infant had been asymptomatic apart from microcephaly noted at 2 weeks of age. Computed tomography of the brain at 4 weeks showed multiple prenatal infarcts. Our case was similar to this in that there was a delay in the evolution of the cerebral symptoms. The head circumference was normal at birth (25th centile) but had fallen to the 10th centile when she was reviewed at 7 months.

Barmada *et al* described two babies who died of cerebral infarcts in association with multiple extracranial thromboemboli, but made no attempt to describe the signs and symptoms noted before death.¹ We know of no reports associating signs of vascular occlusion of a limb at birth with a cerebral infarct and we recommend that infants with such signs should have an ultrasound scan or computed tomogram of the brain.

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Aerosol treatment abuse

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SUMMARY A 4 year old boy with excellent inhaler technique was found to be abusing his salbutamol and beclomethasone dipropionate inhalers. This resulted in aggressive behaviour and probable hallucinations.

Glue sniffing, inhalation of domestic aerosols, and using illegal drugs are becoming common among teenagers but children of preschool age rarely arouse suspicion. We report the case of a 4 year old boy who abused his salbutamol and beclomethasone aerosols.

Case report

A 4 year old boy with asthma was referred to this hospital because he was using his salbutamol and beclomethasone aerosols too often. His three brothers and his father also used beclomethasone and salbutamol aerosols regularly.

At the age of 3½ he became intolerant of his salbutamol Rotahaler capsules and was given salbutamol and beclomethasone dipropionate aerosols. Surprisingly, his technique of using the inhalers was perfect, and we made a video recording of it.

During the previous three weeks at school he had demanded his salbutamol aerosol up to 10 times a day. Administration at home had also increased despite minimal asthmatic symptoms, and he had become increasingly aggressive. His mother had noticed that over a period of three days, four beclomethasone inhalers had been taken from the cupboard and were empty. The following day the precocious 4 year old was found underneath the cupboard, having inhaled one complete aerosol of beclomethasone and half way through his second. He was noted to be agitated, and repeatedly tried to push an imaginary person away from his left ear.

Three months before this, his mother had noted similar changes in behaviour with increased demands for aerosols. Four aerosols were missing from the house. Putting the blame on her older boys she moved the aerosols to a different cupboard: the boy's behaviour improved. On this occasion a change was made to salbutamol and beclometha-

sone Rotacaps with no ill effects, and he had no obvious withdrawal symptoms.

Discussion

Pressurised aerosols had been effective in treating this boy's severe asthma and we were amazed at his competence in using them. His increased use of them at school may well be ascribed to attention seeking, but subsequent draining of aerosols secretly at home was not. As his craving disappeared after changing to a dry powder system, it seems that his craving was not for the salbutamol or the beclomethasone, but for the fluorocarbons used as propellants.

In older children and adults the patient controls his or her own treatment, and monitoring of drug consumption can be difficult; there have been reports of abuse of salbutamol and beclomethasone aerosols in adults.¹ The effects of abuse ranged from euphoria, increase in self confidence, and hallucinations to a report of a grand mal fit.² These effects were also attributed to the fluorocarbons used as propellants. It is important to be aware of aerosol abuse as fluorocarbons may cause cardiac arrhythmias, electroencephalographic changes, and death.⁴ Problems have also been encountered in children; Brennan reported salbutamol aerosol abuse in five children aged 11 to 13.³ Three of the five also took beclomethasone aerosols but did not abuse them.

If abuse of inhalers is suspected, a change should be made to a dry powder system such as Rotacaps and the Rotahaler device, or to a nebulised solution.

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Pledgets in ingrowing toenails

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SUMMARY Eighty children had cotton wool pledgets inserted under the nail corner for ingrowing toenails. Success was achieved in 44 (72%) of the 61 children followed up for a mean of 2.5 years. Appearance was excellent and compliance high. Initial insertion under anaesthesia improved the results, and chronicity did not adversely affect the outcome.

The varieties of treatment, often radical and disfiguring, for ingrown toenails underline the unsatisfactory management of this common, disabling, and underestimated condition.¹ A conservative treatment method would be preferable. Ingrown toenail is common in children and results in loss of school hours, impairment in sports and play, and repeated medical visits. The idea of raising the ingrowing nail edge from the side nail groove, by various methods, is not new, but has been reported only in adults.² We reviewed the use of cotton wool pledgets for ingrown toenail in a paediatric population.

Patients and methods

We reviewed the case histories of patients referred to a single consultant in two paediatric hospitals who had toenail problems during 1979 to 1984, and we selected for study those with ingrown toenail. Their histories, precipitating factors, infection, inpatient stay, acceptability of treatment, and outcome were recorded. Patients were followed up by questionnaire, telephone, and a special follow up clinic.

The treatment used was standard: under general anaesthesia the nail and surrounding skin was cleaned, pus was drained, and the ingrowing nail corner raised by a small, chlorhexidine soaked, cotton wool pledget (figure). Thirty six hours later the pledget was changed. The analgesic, mefenamic acid, was given orally for an hour beforehand. The foot was soaked in chlorhexidine and cetrimide (Savlon), the pledget was removed and a new one reinserted with the help of any fine blunt instrument. The pledget was initially changed twice daily. Subsequent changes were easier, less painful, and did not require analgesia. Children (or parents) were trained in this insertion and allowed home

once they were proficient. Pledgets were continued until the nail had grown beyond the side groove. Success was defined as a painless toenail which was not ingrowing and had a normal appearance.

Results

Eighty patients had pledgets inserted for ingrown toenail during 1979 to 1984. Their age distribution was: 0-4 years, two patients; 5-10 years, 17 patients; 11 years, nine patients; 12 years, 24 patients; and 13 years, 28 patients. The ratio was two boys to one girl. The duration of the ingrown toenail was less than two months in 24 children, greater than two months in 26 children, and of an uncertain duration in 30 children. Right and left sides were equally often affected, and 14 children had bilateral ingrown toenail. The lateral border was twice as often affected as the medial. The mean hospital stay, for treatment and training in pledget insertion, was four days. Altogether 64 patients had general anaesthesia for the initial insertion. Of 10 patients with a history of ingrown toenail, four had had surgery.

The mean duration of follow up was 2.5 years. Sixty one patients were available for follow up, and success was achieved in 44 (72%), 13 required surgery, and four had some remaining problems. Treatment was acceptable to 47 patients (77%), unacceptable to 10 (16%), and uncertain in four. Of 19 patients lost follow up, 10 were doing well when last reviewed, two had failed, one died (of an unrelated cause), and six were of uncertain result.



Figure Infected ingrowing toe nail (left), pledget inserted under ingrowing nail edge (right).

Pledgets failed in 23% of those with initial insertion under anaesthesia compared with 38% in those without anaesthesia. The length of time the child had had the ingrown toenail did not influence success. Appearance was excellent in those attending follow up clinics.

Discussion

This condition receives no attention in most paediatric surgical textbooks. It is mentioned in a book by Filston³ and another cited by Jones and Woodward.⁴ Pledget management is recommended in the latter, but no references are cited and no results reported. Gutter treatment for ingrown toenail in adults achieved success in 20 patients out of 36 studied after a one year follow up and the treatment was proposed for use in general practice.² Other forms of treatment studied include phenol,⁵ cryosurgery,⁶ and radical surgery in adult populations with success varying between 56% and 95%.

In children, ingrown toenail occurs most commonly in the older child (10 to 13 years old), and seems different to the congenital variety. We believe severe cutting or tearing with angling of the edges to be common precipitating factors. Most of our patients had this type of nail at presentation. Friction, trauma, and tight fitting shoes are other possible aetiological factors, yet only 14 of the children we reviewed had bilateral ingrown toenail and the lateral side was most frequently affected.

Children over 7 years old, and parents of those children who were younger, were easily taught to insert pledgets and how to take care of their nails

correctly. Once this had been learned patients could institute treatment for the contralateral nail if or when it became symptomatic (found in two patients).

Failure was reduced (38% to 23%) if the initial insertion was performed under anaesthesia; this was probably due to the thorough cleansing and deep insertion that was possible. The nail edge soon became raised and clear of the soft tissues and subsequent insertions were easy. The appearance was excellent, there was no loss of nail width or soft tissue, and no visible difference between the treated and the contralateral nail.

We propose this form of treatment as an acceptable conservative approach to the management of ingrown toenail in children.

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Acrodermatitis chronica atrophicans

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SUMMARY Two cases of acrodermatitis chronica atrophicans associated with *Borrelia burgdorferi* infection are reported; to our knowledge these are the first cases reported in children.

Lyme disease is a complex multisystem disorder which usually begins with erythema chronicum migrans, a creeping annular erythematous skin lesion. Weeks to months later some patients develop meningitis, cranial or peripheral neuropathies,

myocarditis, or arthritis. The illness is caused by the tick borne spirochete *Borrelia burgdorferi*.¹ Because acrodermatitis chronica atrophicans is also associated with *B. burgdorferi* infection, it is now considered to be a late manifestation of Lyme disease.² Acrodermatitis chronica atrophicans is usually seen in adults aged 30 to 60 years; we now report two cases in children.

Case reports

CASE 1

A 10 year old boy was referred because of darkened

skin over the right lower leg that had been present for a few weeks. No accompanying symptoms such as fever or pain were reported but the boy remembered a tick bite a year before. On examination the skin over the knee, lower leg, and dorsum of the foot was livid with some oedematous and hyperaemic areas. Over the ankle the skin was dry and dystrophic. The erythrocyte sedimentation rate was 22 mm in the first hour, and the white cell count and differential were normal. The *B burgdorferi* titre in the serum was 1/4096 (normal below 1/64).³ Histological examination of a skin biopsy specimen showed a thin epidermis with a strongly pigmented stratum basale and perivascular patchy infiltration by lymphocytes, plasma cells, and histiocytes. Culture of the skin for *B burgdorferi* was negative.² Treatment was started with benzylpenicillin 12 million units/m²/day intravenously for four weeks, and within a week the hyperpigmentation decreased and the oedema and hyperaemia disappeared. Six months later the skin was almost normal. The *B burgdorferi* titre remained high at 1/4096.

CASE 2

A 12 year old boy was referred because of violet



Fig 1 Case 2 before treatment: note hyperpigmentation of left leg with vitiligo like patches



Fig 2 Case 2 six months after treatment with benzylpenicillin; linear streak above knee is a biopsy scar

discolouration of the skin of his left leg. A year earlier the patient had noticed induration of the subcutaneous tissue over the left quadriceps muscle. Later the skin over this area darkened and the lesion spread to the lower leg. There was no pain, functional impairment, or fever, and no history of a tick bite. In addition to this hyperpigmentation and induration of the skin and subcutaneous tissue, a few vitiligo like patches were noted, some of which were atrophic (fig 1). Some areas felt warm. The circumferences of the left upper and lower leg were 2 cm less than the right. The erythrocyte sedimentation rate was 20 mm in the first hour; white cell count and differential were normal. The *B burgdorferi* titre in the serum was 1/4096. Histological examination of the affected skin showed pronounced oedema of the corium, and perivascular patchy round cell infiltrates consisting mainly of lymphocytes. Cultures of the skin for *B burgdorferi* were negative. Treatment was started with benzylpenicillin 12 million units/m²/day for four weeks, and within a week the dark skin areas lightened and the induration decreased. After six months the skin had reverted to normal (fig 2) but the differences in leg circumferences still persisted. The *B burgdorferi* titre in serum remained high at 1/2043.

Discussion

Acrodermatitis chronica atrophicans is a slow progressive disease that runs a biphasic course⁴: the initial or inflammatory stage resembles erythema chronicum migrans, but is clearly differentiated by its diffuse or localised erythema. It usually affects one extremity and later spreads over its extensor surface. In this phase the histology of the skin shows infiltration by plasma cells, lymphocytes, and histiocytes. After periods varying from weeks to months, hyper- and hypopigmentation develop, and gradually the skin becomes frail like cigarette paper so that vessels and subcutaneous tissue become visible; on the other hand fibrosis and sclerosis also develop. In this atrophic or atrophic stage biopsy specimens are pathognomonic showing the typical signs of epidermal atrophy, damaged and degenerated elastin and collagen, and dilated dermal vessels surrounded by plasma cell infiltrates.

In our patients the cutaneous lesions corresponded to the clinical picture of acrodermatitis chronica atrophicans, and the histological findings were compatible with the inflammatory stage of the disease. High antibody titres against *B. burgdorferi* (as found in both our cases) are diagnostic,³ the negative skin biopsy culture is not surprising, because isolation of the organism is notoriously difficult.²

A history of tick bite (absent in case 2) is not mandatory in diagnosing diseases caused by *B. burgdorferi* because the bite is often overlooked or forgotten, and tabanids and mosquitoes may also harbour the pathogen.⁵ Our patients had no other signs or symptoms of Lyme disease.

Benzylpenicillin has been reported to be effective in the inflammatory stage of acrodermatitis, but recommended treatment regimens differ.⁴ Because high doses of penicillin given parenterally have been

successful in the later stages of Lyme disease,⁶ we prescribed intravenous benzylpenicillin 12 million units/m²/day for four weeks. Clinically this treatment was successful, although the skin changes had not completely disappeared at the time of writing. Raised antibody titres may persist for six to 12 months after treatment.³ As in late syphilis, it may be that the time taken to achieve seronegativity after acrodermatitis depends on the duration of the untreated infection.

Our observations show that acrodermatitis chronica atrophicans associated with *B. burgdorferi* may occur in childhood. Paediatricians should therefore be aware of this disorder because early diagnosis and treatment are important.

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Blood counts in extremely low birthweight infants

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SUMMARY White blood, neutrophil, and platelet counts were higher in 101 infants with appropriate weight for gestational age than in 42 infants who were small for gestational age. The recognised

postnatal rise in counts was seen in the infants of appropriate weight, but in the infants who were small for gestational age the counts fell for the first three days.

The results of blood counts in extremely low birthweight infants (<1000 g) may lead to important decisions being taken about the treatment of probable infection, anaemia, or polycythaemia. We report here how extremely low birthweight infants who are either of an appropriate weight for gestational age or small for gestational age have intrinsically different blood counts. A knowledge of these differences may have implications for treatment.

Patients and methods

Blood counts measured during the first 14 days of life in 143 infants who were born consecutively and who weighed less than 1000 g were reviewed (101 of appropriate weight for gestational age and 42 who were small for gestational age). Arterial or venous sampling sites were used as we have previously shown that mean neutrophil counts were similar in blood drawn from these sites and mean haemoglobin concentrations were only slightly higher in venous blood specimens.¹ Blood counts were estimated on a Coulter S+4 counter and the differential white count estimated from smears stained with Jenner-Geimsa. Unpaired *t* tests were used to test the significance of differences between the two groups of babies.

Results

The mean haemoglobin concentration of the group who were small for gestational age at 24 hours (161 (SD 25) g/l) was higher than the group of infants with appropriate weight for gestational age (142 (27) g/l, $p < 0.005$). After this the results were confused by frequent blood transfusions. The mean corpuscular haemoglobin concentration of the group who were small for gestational age (326 (10) g/l) was lower than the group of appropriate weight (331 (18) g/l) on the first day ($p < 0.01$) but the other red cell indices were similar in the two groups.

The mean neutrophil count of the group who were small for gestational age was significantly lower than the group of babies of appropriate weight until the 14th day of life (fig 1). The mean neutrophil count rose immediately after birth in the group of appropriate weight, but fell during the first three days of life in the group who were small for gestational age. In individual babies in this group the fall was so substantial that certain of them became neutropenic ($< 1 \times 10^9/l$). This finding occurred in the absence of infection and in infants in good general health. The mean platelet count of the group of infants who were small for gestational age was significantly lower than in the group of appropriate weight for the first 13 days of life (fig 2). In contrast

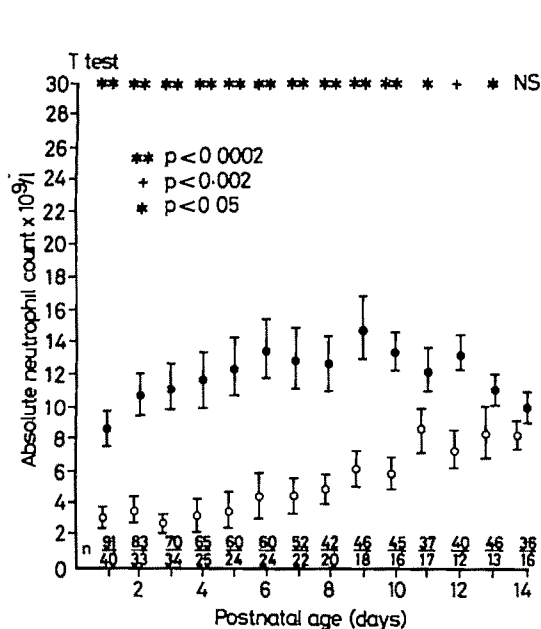


Fig 1 Absolute neutrophil count (SD) during the first 14 days of life in babies of appropriate weight for gestational age (●) and babies who were small for gestational age (○)

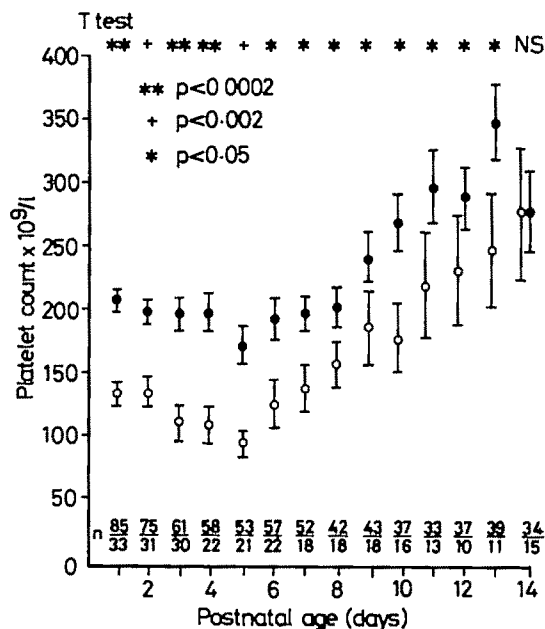


Fig 2 Platelet count (SD) during the first 14 days of life in babies of appropriate weight for gestational age (●) and babies who were small for gestational age (○)

the mean (SD) nucleated red cell count of infants who were small for gestational age was considerably higher at birth ($260 (275) \pm 53 (94) \times 10^9/l$; $p < 0.0001$) and remained so for the first six days of life.

Discussion

Most infants of less than 1000 g birth weight are born vaginally after the spontaneous onset of preterm labour often associated with antepartum haemorrhage or premature rupture of membranes and they are of appropriate weight for gestational age. A minority are born by caesarean section because of severe toxæmia of pregnancy in the mother. The infants born to these mothers are frequently small for gestational age.

Mothers of these two groups of extremely low birthweight infants are likely to be intrinsically different, and they may have had different drug treatments. Mothers with toxæmia may show haemolysis, raised liver enzyme activities, and low platelet counts.² Brazyl *et al* reported that babies born to mothers with severe hypertension had a high incidence of thrombocytopenia, neutropenia, and haemorrhagic complications compared with the babies born to normotensive controls who were retrospectively matched for length of gestation.³ Sibai *et al*, however, in a prospective pair controlled study were not able to confirm this.⁴ In neither of these studies was it possible to elaborate on whether the haematological findings were related to the underlying condition of the mother or the maternal drug treatment. Wicerlov *et al* suggested that maternal hydralazine treatment might cause neonatal thrombocytopenia.⁵

Neutrophilia in the newborn may be seen in neonatal leukaemia where it is almost always associated with chromosome disorders. It has also been proposed that leukaemoid reactions that last for many days after birth may result from maternal steroid treatment. A recent study, however, comparing two matched groups of babies where one group of mothers had been treated with dexamethasone, was unable to show any haematological differences, and the only cases of very high white cell counts were seen in two infants whose mothers had not had steroids and in whom there was no evidence of infection (Thurlbeck and McIntosh, in preparation).

It is usually postulated that the higher haemoglobin concentration seen in infants who are small for gestational age is due to chronic intrauterine hypoxia. We know of no studies on the marrow of such infants, but it is possible that the lower white cell and platelet counts observed in these babies in the current study could be due to marrow stem cells

being more committed in utero to producing cells of the red cell series in an attempt to improve oxygen transport and delivery in the fetus. At birth it may not be possible for the stem cells to switch immediately to white cell and platelet production. Some evidence supporting this theory is the significantly raised nucleated red cell count during the first six days of life in the group who were small for gestational age. It was only when the nucleated red cell count fell that the peripheral white count and platelet count rose.

The purpose of this paper is to draw attention to differences in the blood counts of these two groups of extremely low birthweight babies, not to account for them. We believe that the differences are so spectacular in the first week of life that it may be important to anticipate them. For example, babies who are small for gestational age often have profound neutropenia, and despite the fact that they are born by caesarean section with no predisposition to infection it may be reasonable to give them prophylactic antibiotics in the same way as one would to other neutropenic immunocompromised patients. One infant early in this study, who was born with a neutrophil count of $0.8 \times 10^9/l$, suddenly developed a rapidly fatal septicaemia on the 4th day of life. In retrospect his neutrophil count had fallen steadily after birth and we believe that he developed septicaemia because of neutropenia, not the reverse. We have not seen any complications directly resulting from the thrombocytopenia but have on several occasions felt obliged to perform clotting screens to ensure that the thrombocytopenia was not part of disseminated intravascular coagulation.

We would like to thank the staff of the neonatal unit for care of the infants and the staff of the haematology department for their excellent service to our unit. A full table of results is available from N McIntosh.

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Patient triggered ventilation in premature neonates

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SUMMARY Patient triggered ventilation using oesophageal pressure changes was assessed in eight premature neonates. Respiratory activity was reliably recorded and positive pressure inflation occurred synchronously with inspiration. Peristalsis resulted in only minimal interference. During patient triggered ventilation, inflating volume and oxygenation increased significantly compared with periods of conventional ventilation.

Synchronous respiration with artificial ventilation in premature neonates improves oxygenation,¹ but attempts to achieve such a response by imposing a standard rate are not always successful.² Patient triggered ventilation—the delivery of positive pressure inflation initiated only by respiratory efforts—ensures synchrony but until recently was not practical in preterm neonates. A recent report suggested that it was possible to modify a conventional neonatal ventilator so that it could be triggered even by preterm infants' respiratory efforts.³ Changes in abdominal expansion were used to detect respiration,³ but these signals may be confused by gross body movements. During mechanical ventilation, oesophageal pressure changes were shown to be reliable in detecting respiratory efforts, and they were not affected by ventilator pressure changes or by postural movements.^{1,4} The aims of the present study were to investigate the apparent success of triggered ventilation in preterm neonates and to assess the effect of oesophageal pressure changes as the trigger.

Patients and methods

Eight patients with the respiratory distress syndrome were studied; all were less than 1 week old with a mean gestational age of 27 weeks (range 24–31). Ventilatory support was given by an SLE Newborn 250 ventilator. Ventilator settings were determined before the study by the clinician in charge of the infant; rates varied from 50–80/minute, and peak inspiratory pressures from 14–24 cm H₂O. No infant was either paralysed or sedated, but those on ventilators with rates of less than 30/minute were treated with a methylxanthine.

Permission for the study was given by the hospital's ethics committee.

Infants were entered into the study as soon as they had been stable on conventional ventilation for at least two hours. They were then switched to continuous positive airways pressure trigger ventilation for at least 30 minutes. Trigger ventilation was discontinued if the infant was either apnoeic for longer than 20 seconds, or failed to trigger a ventilator pulse during that time.

Patient triggered ventilation was delivered by a modified SLE Newborn 250 ventilator. The ventilator has a manual breath control which, when set for continuous positive airways pressure, permits delivery of a single positive pressure inflation of the same magnitude and duration as that predetermined during intermittent positive pressure ventilation. Only if a critical change in oesophageal pressure is exceeded (increase in negative pressure swings) is the manual breath control triggered (a systems delay of up to 100 milliseconds is possible).

Throughout periods of patient triggered ventilation and the preceding and succeeding 30 minute periods of conventional ventilation we recorded transcutaneous oxygen tensions, inflating volume, and ventilator and oesophageal pressure changes using the techniques previously described.^{1,2,4} From the oesophageal pressure record we calculated the change in pressure necessary to trigger the ventilator, the infant's respiratory rate, and the number of periods of apnoea and peristalsis. Ventilator rate and inflating volume during different types of ventilation were compared, as was the mean transcutaneous oxygen tension during the final 10 minutes of each 30 minute period.

Statistical analysis was by paired Student's *t* test.

Results

Oesophageal pressure changes of 0.3–0.5 cm H₂O triggered the ventilator; these were greater than the pressure change from the cardiac artefact. Only one infant who had previously been apnoeic had periods of respiratory efforts that were not strong enough to trigger the ventilator. Apnoeic periods were infrequent despite the fact that three of the infants had previously been fully ventilated. The longest period of apnoea was 18 seconds and occurred in an infant

Table Comparison of conventional and patient triggered ventilation. Figures are mean (range)

Measurement	Conventional ventilation	Triggered ventilation
Tidal volume (ml)	6.3 (5-11)	8.2 (5.6-12.3)
Delivery rate of inflating pressure		
Conventional rate ≥ 60 breaths (n=3)	72 (50-80)	78 (72-90)
Conventional rate < 60 breaths (n=5)	17 (15-50)	45 (30-52)

previously on a rate of five breaths/minute. Otherwise, apnoeic episodes varied in length between two and 10 seconds and were less than one per minute. Peristaltic waves did not trigger the ventilator, but did interfere with the signal. This was only a problem in three infants, and then only for the first two minutes. The table shows that in seven of eight infants the inflating volume increased significantly during triggered ventilation ($p < 0.02$). Delivery of inflating pulses increased in all previously ventilated infants at a rate of less than 60 breaths/minute. Transcutaneous oxygen tensions increased during triggered ventilation in all infants when compared with both periods of conventional ventilation (mean increase 12 mm Hg, range 5-37 mm Hg, $p < 0.01$).

One infant remained on triggered ventilation for a total of three hours. After only 15 minutes his PaO_2 rose from 67 to 87 mm Hg with an increase in inflating volume of 11-12.3 ml when compared with conventional ventilation. Peak inspiratory pressure was gradually reduced from 14-10 cm H_2O with maintenance of arterial blood gases (pH 7.27, PaCO_2 36 mm Hg, and PaO_2 67 mm Hg at 14 cm H_2O on conventional ventilation; and pH 7.27, PaCO_2 38, PaO_2 84 mm Hg at 10 cm H_2O after one hour of triggered ventilation).

Discussion

Our results support previous findings that patient triggered ventilation, even in very premature infants, can be successful³: oxygenation improved, partly due to an increase in inflating volume during triggered ventilation. This increase reflected the difference in the infants' respiratory efforts—synchrony during trigger mode, but asynchrony and limitation of inflation during conventional ventilation. In infants who had been ventilated at a rate of less than 60 breaths/minute the improvement in oxygenation was also due to the increase in the number of inflations delivered during triggered ventilation.

Small changes in oesophageal pressure successfully triggered positive pressure inflation. To decrease the frequency of ventilator breaths trigger sensitivity had to be reduced. The variation in the strength of respiratory efforts was insufficient to be certain that positive pressure inflation was delivered only on a certain number of respiratory efforts. Ideally—to facilitate weaning—triggering from a preselected number of breaths (regardless of size or frequency) should be incorporated into the ventilators as with 'adult' servo-ventilators.

The oesophagus has the advantage as a trigger site that gross body movements are not registered as pressure changes which could trigger the ventilator. Peristaltic activity, a theoretical disadvantage of this site, caused relatively few problems but these could be increased by the pooling of saliva after prolonged use. Both trigger sites studied to date—oesophagus and abdomen—³ have a major disadvantage in that they fail to differentiate between obstructive and non-obstructive respiratory efforts and fail to set off the alarm during obstructive episodes despite the absence of air flow.⁵

We conclude that patient triggered ventilation can be successful, particularly during weaning. By conversion to synchronous respiration oxygenation was improved and thus might reduce the incidence of pneumothoraces.² Using changes in air flow as the trigger could be advantageous, as this is a more accurate indicator of both respiratory efforts and apnoea. This is currently being investigated.

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Copper and very low birthweight babies

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SUMMARY Serum concentrations of copper and ceruloplasmin were measured in 24 very low birthweight babies. They were high in those weighing less than 1000 g, and critically ill or receiving intravenous nutrition, and normal in those with bone disease, neutropenia, or oedema. Care is needed to maintain adequate concentrations without toxicity.

Copper is an essential trace element found in several metalloenzymes, including lysyl oxidase, cytochrome C oxidase, and superoxide dismutase. As the survival of infants born at less than 28 weeks' gestation has increased a new population is growing up that is at risk of copper deficiency because of low body stores and artificial feeding. The aim of this study was to measure serum copper and ceruloplasmin concentrations in very low birthweight (VLBW) babies to find out whether copper given intravenously is metabolised, and whether deficiency can be detected by the methods that we used.

Patients and methods

Twenty four VLBW babies were studied. Their mean gestational age was 28 weeks (range 24–35) and mean birthweight 1088 g (range 650–1460 g); 12 were boys and three were small for gestational age. Total parenteral nutrition was started on day 3 and fat emulsion (Intralipid, KabiVitrum) was introduced on day 5. Amino acids were given as Vamin. Small amounts of breast milk were given if tolerated. The total parenteral nutrition supplied 0.22 $\mu\text{mol/kg}$ copper (Ped-El, KabiVitrum), 1.00 mmol/kg calcium, 1.16 mmol/kg phosphate and 200 U vitamin D daily. When the babies were having enteral feeds, multivitamins (including 800 U vitamin D) were prescribed from 2 weeks of age, with an additional 1000 U of vitamin D for those whose birthweight had been less than 1000 g. Breast fed babies weighing <1200 g were given a neutral sodium phosphate supplement (1 mmol/kg/day). The calculated intakes of copper in babies receiving full enteral feeds were 0.63–1.23 μmol and 1.13–1.5 $\mu\text{mol/kg/day}$ on breast milk and formulae feed, respectively. One baby received maintenance treatment with frusemide for chronic lung disease.

Albumin low in salt was infused in all babies with serum albumin concentrations of less than 20 g/l.

A sample of 0.2 ml serum was diluted in 0.8 ml molar hydrochloric acid for copper analysis by atomic absorption spectrophotometry (Instrumentation Laboratories AA/AE 257). Standards ranged from 1–17 $\mu\text{mol/l}$. All glassware and test tubes were soaked in 0.1 M hydrochloric acid for a minimum of one day and rinsed three times in deionised water. A sample of 0.1 ml serum was frozen for ceruloplasmin analysis by immunoradial diffusion. Babies who had been transferred to another hospital or home did not have all the samples taken. X ray pictures of the babies knees were taken and determinations of plasma alkaline phosphatase activity and phosphorus concentration were made as a routine. The x-ray pictures were reviewed by a radiologist (LMcD) who had no clinical information about the babies, and bone disease of prematurity was diagnosed if there were signs of osteopenia and metaphyseal changes.

All results are given as mean (SEM) and analysed using Student's unpaired *t* test and least squares linear regression.

Results

There was no correlation between gestational age and serum copper concentration at 1 week ($r=0.01$). Babies with birth weights of less than 1000 g had higher serum copper concentrations at 1 week than those with birth weights of 1000–1500 g: 13.1 (1.9) μmol ($n=7$) and 8.9 (0.8) $\mu\text{mol/l}$ ($n=12$) ($p<0.05$). There was no significant change with postnatal age, the mean serum copper concentration at 1 month being 10.7 (0.7) $\mu\text{mol/l}$.

As the concentrations did not change with postnatal age concentrations at 1 week and 1 month were combined and the effect of feeding determined. Babies receiving parenteral feeds had significantly higher serum copper concentrations than babies receiving full enteral feeds ($p<0.005$).

Serum concentrations of ceruloplasmin correlated with those of serum copper ($r=0.89$, $p<0.001$). The mean ceruloplasmin:copper ratio was 0.19 (range 0.08–0.24). Four babies had high serum copper concentrations (18.8–20.9 $\mu\text{mol/l}$); all were receiving total parenteral nutrition and critically ill (with necrotising enterocolitis, septicaemia, and intracra-

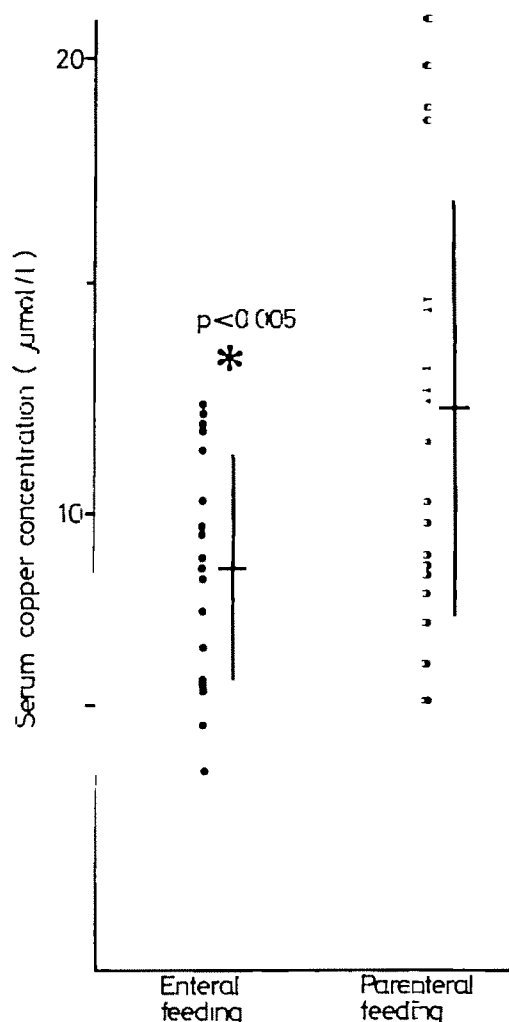


Figure Mean (SD) serum copper concentrations in very low birth weight babies fed enterally and parenterally.

nial haemorrhage) and their ceruloplasmin:copper ratios were 0.13–0.23.

There was no difference in the serum copper concentrations at 1 month between those babies with and without bone disease, mean concentrations being 11.4 (1.3) $\mu\text{mol/l}$ ($n=9$) and 10.1 (1.5) $\mu\text{mol/l}$ ($n=9$) respectively. As expected, the mean maximal alkaline phosphatase activities were higher in those infants with metabolic bone disease 487.9 (55.3) ($n=9$) compared with 297.5 (33.6) IU/l ($n=6$) ($p<0.05$); there was no correlation between alkaline phosphatase activity and copper concentration. The mean minimal serum phosphorus concentrations in those infants with and without bone disease were

1.36 (0.02) and 1.55 (0.57) mmol/l, respectively. Five babies were neutropenic ($<1 \times 10^9/\text{l}$) and septic, and their mean copper concentration at 1 month was 12.5 (2.3) $\mu\text{mol/l}$. There was no association between low serum copper concentrations and oedema. Seven babies required albumin infusions; their mean copper concentration was 11.8 (4.9) $\mu\text{mol/l}$ and in all the oedema resolved after the infusion.

Discussion

Serum copper concentrations at 1 week did not correlate with gestational age, and there was no significant change with postnatal age. Babies with birth weights of <1000 g had significantly higher copper concentrations than those with birth weights of ≥ 1000 g, which probably reflects the frequent use of total parenteral nutrition in these babies as babies receiving total parenteral nutrition had higher mean serum copper concentrations. This could have been due to injury to the hepatobiliary system, as copper is excreted in the bile. Stress and infection are other possible causes, as are frequent blood transfusions.

As 93% of intravascular copper is bound to ceruloplasmin, possibly more important than a high serum copper concentration is the effect of any factor that might reduce the ceruloplasmin:copper ratio, thus increasing the diffusible copper fraction. Only one of our 24 VLBW babies had a reduced ceruloplasmin:copper ratio.

Copper deficiency reflected in apnoea, bone disease, oedema, anaemia, and neutropenia has previously been described in preterm infants between 8 weeks and 6 months of age.^{1,2,3} We found no evidence of it in our small sample studied at 3 months; there was a high incidence of subclinical metabolic bone disease but no evidence that this was due to copper deficiency. Recently, Sutton *et al* described four preterm infants who developed clinical copper deficiency with low plasma copper concentrations;⁴ they were receiving formula containing 0.61 $\mu\text{mol/l}$ whereas our formula, like most commercial formulas, contained 0.80 $\mu\text{mol/l}$ copper. The copper concentration of breast milk is lower, but the copper is more bioavailable.

In conclusion, parenteral nutrition containing 0.2 $\mu\text{mol/kg/day}$ and infant formulas with a copper concentration of 0.80 $\mu\text{mol}/100$ ml provide enough copper to maintain serum copper concentrations and prevent the clinical signs of copper deficiency. Serum copper reflects only a small fraction of total body copper, however, and is probably a poor reflection of the amount in the body. Measurement of enzymes dependent on copper (such as superoxide dismutase) may be more helpful.

Current recommended doses range from 0.10–1.48 $\mu\text{mol/kg/day}$,^{4,5} and some recommend that copper be excluded completely from short term parenteral nutrition.⁶ Our experience suggests that potentially toxic concentrations of copper can be achieved in critically ill preterm infants and that intravenous copper supplements should be withheld until the babies are stable, and then their serum copper concentrations should be monitored. Further studies are needed to define optimal intravenous copper requirements.

We are grateful to Dr RPH Thompson, Dr B Slavin, and Professor JW Scopes for their support

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Maternal narcotic abuse and the newborn

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SUMMARY In 50 infants born to women who continued to take heroin during all or part of their pregnancy the drug withdrawal symptoms were mild and were noted in 21 infants (42%). Only nine infants required treatment. Sudden infant death syndrome occurred in two infants at 4 and 6 months.

An increasing number of infants are being born to mothers addicted to narcotic drugs. Reports about the effects of maternal drug abuse on the infant are conflicting. Previous series, largely from North America, have reported increased neonatal mortality and morbidity in these infants.^{1,2} Recently, Klenka reported minor withdrawal symptoms in more than 70% of infants but noted a low incidence of severe symptoms.³ This was attributed to smoking heroin rather than to intravenous abuse. In order to ascertain the current risk we studied 50 infants born between 1983 and 1986.

Patients and methods

During the study period, 44 women known to be addicted to narcotic drugs delivered 50 infants in two Glasgow maternity hospitals. One mother had a twin pregnancy, and five women delivered twice

during this period. The combined annual delivery rate in these two hospitals is roughly 6000.

All except one of the mothers were using heroin, either alone or in combination with a variety of other drugs. The one exception was a methadone addict. The mean (SD) duration of addiction before delivery was 2.7 (1.5) years. The amount of heroin used varied widely and was difficult to ascertain. Most of the women (75%) were intravenous heroin abusers; the rest either smoked or snorted the drug. Twenty four women had partners who were also drug addicts.

The ages of the mothers ranged from 17–34 years: mean (SD) 21.5 (3.4). All were offered routine antenatal care with the addition of an inpatient detoxification programme. Nineteen of the women had little or no antenatal care, and two concealed their pregnancies.

The infants were admitted routinely to the special care nursery after delivery and were observed for signs of drug withdrawal for 48 hours. Symptomatic infants remained under close observation. Treatment was initiated if there were constant tremulous movements, convulsions, or a disturbed sleep or behavioural pattern such as restlessness or crying within one hour of a feed. The drugs used in treatment were phenobarbitone, chloral hydrate, and phenobarbitone either singly or in combination depending on the individual clinician.

Results

Signs of drug withdrawal were noted in 21 infants (42%) (table 1). In most of the infants these were mild but nine (18%) had symptoms considered sufficient to warrant treatment. Five had late or prolonged withdrawal symptoms with irritability and excessive hunger.

The birth weight of affected infants ranged from 1.1–3.54 kg; mean (SD) 2.77 (0.58). Neonatal problems, other than drug withdrawal symptoms, in the infants of addicted mothers are documented in table 2. In 19 pregnancies there had been little or no antenatal care and 11 (57%) of them resulted in preterm delivery. Thirty nine (78%) of the infants were discharged home, eight under supervision orders. Nine were discharged to foster care, and two were accepted.

Few of these children were followed up successfully. Most failed to attend outpatient appointments. Three are known to have long term problems. One child is microcephalic and severely handicapped, one has a cleft palate, and one is deaf. There were no neonatal deaths in this group. Two infants suffered sudden infant death syndrome at 4 and 6 months.

Table 1 *Drug withdrawal symptoms in 21 affected infants*

Symptom	No of infants (%)
Jitteriness	21 (100)
High pitched cry	11 (52.4)
Snuffles	10 (47.6)
Sleep disturbance	9 (42.9)
Vomiting	6 (28.6)
Abnormal feeding pattern	5 (23.8)
Tachypnoea	4 (19.0)
Fever/excess sweating	1 (4.8)
Convulsions	1 (4.8)

Table 2 *Neonatal complications occurring in infants (n=50) of addicted mothers*

Complication	No of infants (%)
Preterm delivery (<37 weeks)	14 (28)
Small for gestational age	14 (28)
Occipitofrontal head circumference <10th centile	17 (34)
Delivery by caesarean section	3 (6)
Delivery by forceps	7 (14)
Fetal distress (cardiotocographic changes with or without meconium staining)	15 (30)
Apgar scores <6 at one minute	14 (28)
Idiopathic respiratory distress syndrome	2 (4)
Required assisted ventilation	3 (6)

Discussion

The incidence and severity of drug withdrawal symptoms in the group of infants studied is lower than previously reported in infants of narcotic addicts. Klenka attributed a reduced severity of symptoms to low dose exposure in mothers who smoked rather than injected heroin.³ In our series, however, 75% were intravenous drug abusers.

Alterations in the severity of symptoms may reflect changing patterns of drug taking: most addicts now take more than one drug. The infant may be affected not only by exposure to heroin but by the other drugs taken. It is well recognised that methadone results in more prolonged withdrawal symptoms. Most mothers in our series were using heroin in combination with other drugs but few were using methadone on a regular basis.

No neonatal deaths occurred in our series. There were two cases of sudden infant death syndrome; an increased incidence has been previously reported in infants of drug addicts.⁴ In keeping with previous reports, we noted suboptimal intrauterine growth, including head growth, in many infants.⁵ This may relate as much to other factors in the lifestyle of the addict as to intrauterine heroin exposure. Smoking, poor diet, and poor antenatal care, all associated with poor fetal growth, are common in these mothers. Where there was little or no antenatal care we noted an increased risk of preterm delivery. This is well recognised in non-addict populations. Perhaps efforts to improve the outlook for these infants should be directed at encouraging the use of antenatal care resources.

The ability of the drug addict to care for her child after discharge is of major concern. Many addicts have unstable backgrounds with no family support. An early assessment of the family and support available to the mother is essential. Debate continues about the long term outlook for these children; there are reports of an increased incidence of behaviour problems and learning difficulties.⁶ Due to difficulties with follow up we were unable to explore this.

No mother in our group was positive for human immunodeficiency virus. With the increasing prevalence of this virus this may well become one of the major risks to these infants in the future.

In conclusion we report a low incidence of severe drug withdrawal symptoms requiring treatment in infants born to drug addicted mothers. The main risks were associated with the mother's lifestyle as a drug addict rather than a direct effect of the drugs.

We thank our obstetric and paediatric colleagues for allowing us to report on their patients and Miss A Campbell for typing the manuscript.

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Neonatal infections with *Haemophilus* species

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SUMMARY During a 27 month study seven non-serotypable strains of *Haemophilus influenzae* and two of *Haemophilus parainfluenzae* were isolated from nine neonates. Seven had early infection associated with respiratory distress or conjunctivitis; three had septicaemia one of whom died. The incidence of haemophilus septicaemia was 0.23 per 1000 live births.

The number of reports of infections caused by non-serotypable *Haemophilus influenzae* during the neonatal period is increasing.¹ Any series that includes only cases of bacteraemia or meningitis is likely to under report characteristic clinical features of infection with this organism.² We report a study conducted over 27 months of all haemophilus isolates in one unit.

Material and methods

On 1 January 1985 surveillance of haemophilus infections in our neonatal unit started and we report the results until 31 March 1987. When systemic sepsis was suspected we took samples of blood, urine, cerebrospinal fluid, nose, throat, umbilical, and rectal swabs before starting antibiotics. In addition, endotracheal secretions from babies requiring assisted ventilation were routinely cultured three times a week.

Blood cultures were performed using brain heart infusion broth with and without sodium thioglycolate (Gibco Ltd) with routine subculture to chocolate agar after 48 hours and five days' incubation at 37°C. *Haemophilus* spp were initially identified by their growth and morphology on chocolate agar

after primary culture or following enrichment in cooked meat medium. Strains were speciated and biotyped according to the method of Kilian using laboratory prepared media.³ Slide agglutination was used to attempt to serotype the strains using type specific antisera prepared by the Public Health Laboratory Service (type b) and Wellcome (types a, c, d, e, and f).

Antibiotic sensitivities were performed and interpreted using the comparative method.⁴ To prepare the inoculum six isolated colonies were touched and added to 2.5 ml of 1% tryptone water (Oxoid). *H influenzae* NCTC 11931 was used as the control organism. The test medium was Isosensitest (Oxoid) with 5% saponin lysed horse blood (Tissue Culture Services) and 10 mg/ml β nicotinamide adenine dinucleotide grade III (Sigma). Incubation was performed at 37°C in a 5% carbon dioxide incubator. Disc contents (measured in μ g) were ampicillin 2, cefuroxime 30, gentamicin 10, netilmicin 30, neomycin 10, trimethoprim 1.25, chloramphenicol 10 (Oxoid) and polymyxin B 250 units (Mast Laboratories Limited). The presence of β lactamase was detected with Intralactam strips (Mast Laboratories Limited).

Results

Throughout the study there were 12 910 live births in the hospital. The characteristics of the nine babies with *Haemophilus* are shown in the table. All neonates were born by spontaneous vertex delivery, except cases 1 and 9 who were delivered by caesarean section. Cases 1 and 2 grew *H influenzae* and *H parainfluenzae*, respectively, from respiratory secretions at 3 weeks of age. These were probably nosocomial infections as the two babies were not

Table Clinical details of nine cases infected with *Haemophilus* spp

Case No	Sex and gestational age (weeks)	Birth weight (g)	Risk factors for early onset sepsis, [duration of membrane rupture — hours]	Clinical diagnosis	Outcome	Site of positive culture
1	M, 29	570	Note [0]	Right upper lobe pneumonia, chronic lung disease	Recovered	Endotracheal aspirate
2	F, 23	960	Spontaneous premature rupture of membranes [4]	Asymptomatic; recovered from severe respiratory distress syndrome	Recovered	Nasopharyngeal aspirate
3	F, 35	2660	Spontaneous premature rupture of membranes, maternal fever, antepartum haemorrhage six weeks earlier + small bleeds since 2]	Mild respiratory distress syndrome	Recovered	Gastric aspirate, nose, throat, naso-pharyngeal aspirate, placenta
4	M, 24	700	Spontaneous premature rupture of membranes [5]	Severe respiratory distress syndrome	Died, intraventricular haemorrhage; capsular liver tear at post mortem; early fetal pneumonia	Gastric aspirate, blood
5	F, 24	790	Spontaneous premature rupture of membranes; maternal fever [17]	Severe respiratory distress syndrome	Recovered	Blood, rectum, placenta, maternal vagina
6	F, 33	2210	Maternal fever [2]	Conjunctivitis	Recovered	Conjunctiva, blood, gastric aspirate, maternal vagina
7	M, 33	1960	Spontaneous premature rupture of membranes [2]	Conjunctivitis	Recovered	Conjunctiva
8	M, 34	2430	Spontaneous premature rupture of membranes [2]	Conjunctivitis	Recovered	Conjunctiva, gastric aspirate, placenta, maternal vagina
9	M, 41	3260	Prolonged rupture of membranes, antepartum haemorrhage, maternal fever vaginal loss for two weeks	Conjunctivitis	Recovered	Conjunctiva, nose, throat, rectum, ears, umbilicus, placenta

colonised at birth. The remaining seven patients presented on the first day of life, and maternal specimens received from five of these patients yielded a *Haemophilus* of the same biotype.

There were two patients with *H parainfluenzae*, (cases 2 and 9). Case 2 was probably asymptotically colonised with the organism and case 9 had conjunctivitis. The other seven babies grew *H influenzae*, and all the isolates were non-capsulate. They comprised biotype I (n=1), II (n=2), III (n=2), V (n=1), and unknown (n=1).

Three babies (cases 4, 5 and 6) had septicaemia

and received penicillin and gentamicin, ampicillin and netilmicin, and ampicillin, respectively. Two presented with clinical and radiological features indistinguishable from hyaline membrane disease, and case 4 died on day 2, pneumonia being confirmed at necropsy. The third septicaemic baby had bilateral conjunctivitis at birth but was otherwise well. The four cases of conjunctivitis were treated with trimethoprim and polymyxin B eye drops and all resolved.

All strains examined were sensitive to neomycin, gentamicin, cefuroxime, and polymyxin B, but two

were resistant to chloramphenicol, one to ampicillin due to the production of β lactamase, and one to trimethoprim.

Discussion

The number of reports of *H influenzae* sepsis in the newborn has increased. In one study *H influenzae* caused 1.4% of cases of neonatal sepsis seen in the early 1960s, rising to 3.8% over the next 10 years.² In a study from Houston the proportion rose from 0.3% in the early 1970s to 2.6% over the next five years. The incidence of neonatal haemophilus bacteraemia in 1976-81 in Houston was 0.14 per 1000 live births,¹ and we found an incidence of 0.23. Any apparent increase, however, may be due as much to increased awareness as to a true rise in incidence.

One study described 10 cases of neonatal bacteraemia due to *H influenzae*, and in four cases biotype IV was isolated.¹ Non-serotypable strains are rarely biotype IV unless they are of neonatal, maternal, or genital origin. Non-serotypable strains belonging to biotype IV may have a special affinity for the genital tract.¹ Biotypes II and III have also been isolated from cases of neonatal sepsis. In contrast, we found several biotypes but no cases due to biotype IV.

Early neonatal sepsis with haemophilus is likely to arise by maternal vaginal carriage. The reported rate of vaginal carriage during pregnancy is less than 1%.¹ If the incidence of neonatal sepsis due to *Haemophilus* continues to rise there may be a case for introducing selective media to increase its detection from vaginal swabs, as is used for sputum bacteriology.

Ophthalmia neonatorum is a common condition and occurred in 12% of newborn babies in Southampton and 8.2% in Harrow.⁵ In the Southampton study three of 42 patients grew *Haemophilus* spp (two *H influenzae* and one *Haemophilus* spp), but in Harrow the organism was not isolated. In most studies in developed countries about one third of cases of neonatal conjunctivitis are associated with bacterial pathogens other than *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

When this occurs, it is usually treated with neomycin or chloramphenicol eye drops.⁵ Chloramphenicol resistance occurs in up to 1% of non-capsulate *H influenzae*, although it is rarely found among capsulate strains.⁶ Two strains in our series (*H influenzae* and *H parainfluenzae*) were chloramphenicol resistant. Standard first line antibacterial treatment for sticky eye in Oxford was trimethoprim and polymyxin B sulphate eye drops because an endemic *Klebsiella oxytoca* strain, which was chloramphenicol, neo-mycin, and gentamicin resistant, often colonised babies in our unit.

Penicillin or ampicillin and an aminoglycoside are often used in the treatment of neonatal infection of unknown cause. Only one strain of *H influenzae* in this study was a β lactamase producer, and ampicillin resistant strains of *H influenzae* are fortunately uncommon in this setting.¹ A change of standard empirical antibiotic treatment is not indicated by the results of this study, except if a baby fails to respond.

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Ultrasound diagnosis of nephrocalcinosis in preterm infants

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SUMMARY The incidence of nephrocalcinosis in very low birthweight (less than 1500 g) premature infants was assessed by ultrasound scan and analysis of urine. Three of 36 infants had nephrocalcinosis. All had been receiving long term frusemide for bronchopulmonary dysplasia with simultaneous fluid restriction. Urinary investigations showed no consistent findings in babies with nephrocalcinosis.

The survival of very low birthweight premature infants has improved in the last 10 years as advances in the understanding of diseases and their treatment have been made. Multiple drug treatment is often required, and metabolic disturbances are common.

As more infants survive, a larger number who initially required assisted ventilation and increased oxygen concentrations develop chronic lung disease which requires long term oxygen supplements. Frusemide is sometimes used for several months while the babies are dependent on oxygen. The oral dose ranges from 2–3 mg/kg/day. Side effects include hyponatraemia, hypokalaemia, hypochlor-aemic metabolic alkalosis and hypercalciuria.¹ Urinary calcium excretion is increased 10-fold² and this is thought to be the major factor in the development of nephrocalcinosis and nephrolithiasis.³ The total dose may also be important. Osteopenia, from which premature infants are at risk, is also exacerbated.

Early studies used abdominal radiographs to detect nephrocalcinosis²; more recent reports have shown that real time ultrasound is considerably more sensitive.³ Ultrasound pictures show nephrocalcinosis as areas of increased echo production in the medullary pyramids. They may also detect associated renal calculi.

Patients and methods

Infants admitted to the neonatal unit at the Queen Victoria Hospital with birth weights of ≤ 1500 g born between 1 September 1983 and 30 July 1984 were included in the study.

At 12 months of age all infants had ultrasound

scans of the urinary tract with a real time sector scanner using a 7.5 MHz or 5 MHz transducer. Parasagittal and coronal views of the kidneys were routinely taken, and the coronal views usually provided the best definition of the anatomy of the kidney.

A spot sample of urine was centrifuged and examined by phase contrast microscopy. An aliquot was simultaneously frozen for batch analysis of osmolality, and calcium, creatinine, and β -2-microglobulin concentrations using the Phadebas radioimmunoassay (Pharmacia Diagnostics).

Results

Twenty eight of 64 infants were excluded, 20 because of geographical isolation, and eight because the parents did not give consent.

Two of four infants who weighed less than 1000 g at birth and one of 32 who weighed between 1000 and 1501 g at birth had nephrocalcinosis. The dose of frusemide that had been given to the three with nephrocalcinosis varied from 2 to 8 mg/kg/day. The total doses in the individual infants ranged from 220–630 mg. All three were on fluid regimens of less than 160 ml/kg/day for at least 80% of the time that they were receiving frusemide. None had received chlorothiazide. Of the 33 infants who did not have nephrocalcinosis, the total frusemide dose in individual infants ranged from 0–305 mg; only two received more than 100 mg. Both received more than 170 ml/kg/day of fluid.

In the intensive care unit management (including nutrition and vitamin supplementation) is standardised. There was no difference between the infants with and without nephrocalcinosis in the amount of vitamin D supplementation, or the type of milk mixture they received, or the incidence of osteopenia of prematurity or prolonged acidosis and hypercalcaemia, or the administration of other drugs.

Urinary β -2-microglobulin was within the normal range (0–375 ng/ml) in all infants. Urinary calcium: creatinine ratio (mmol: mmol) ranged from 0.033–3.68 (normal <0.6) and this did not correlate in any way with nephrocalcinosis. Microscopy of the urine did not show any haematuria or other abnormalities.

in any infant, and osmolality and pH varied, but there were no associations between any measurement and nephrocalcinosis.

In two of the three infants the nephrocalcinosis resolved. In one it disappeared after 16 months when the frusemide was stopped. In the second it disappeared after five months' treatment with chlorothiazide. The third died of unrelated causes and necropsy was not performed.

In addition to the three infants with nephrocalcinosis, five were found to have structural abnormalities of the urinary tract on ultrasound scans.

Discussion

Ultrasound scanning has proved to be a useful and effective means of diagnosing nephrocalcinosis. Correlation of results of ultrasound scanning before death and histology at necropsy has confirmed the association between increased echogenicity of medullary pyramids and nephrocalcinosis.² (figs 1 and 2). The greater sensitivity of modern ultrasound equipment in diagnosing nephrocalcinosis suggests that early reports may have underestimated its incidence.² Nephrocalcinosis is associated with hypercalcaemia and hypercalciuria, hypervitaminosis D, primary hyperoxaluria, distal renal tubular acidosis, and Bartter's syndrome. It also occurs in premature infants on long term frusemide treatment, and in children taking vitamin D and phosphate for X-linked hypophosphaturic rickets. It has recently been observed in association with a hypoprostaglandinuric tubular syndrome with hypercalciuria and hypokalaemia in preterm infants.⁴

The earliest calcium deposits appear as an echogenic rim at the periphery of the medullary pyramids with a preserved echolucent centre. As the disease progresses the entire medullary pyramid becomes echogenic.⁵

Nephrocalcinosis should be differentiated from other causes of increased echogenicity of medullary pyramids. During the neonatal period oliguria associated with medullary hyperechogenicity may indicate the transient acute tubular disease that is due to deposition of Tamm-Horsfall glyco protein. Several earlier case reports of nephrocalcinosis may have been describing this disease,⁶ as follow up ultrasound scans were not always done. Differentiation between the two diseases is possible if the ultrasound examination is repeated after two weeks. In transient echogenicity the echogenic regions resolve over days, whereas nephrocalcinosis takes months. Recessive polycystic renal disease may produce a pattern of echogenic pyramids in children, but in infants the kidneys are usually

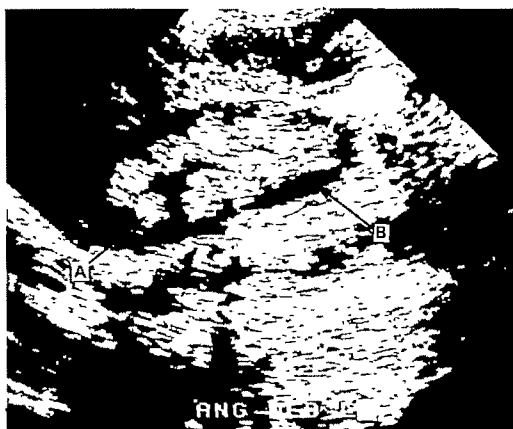


Fig 1 Renal ultrasound picture showing medullary nephrocalcinosis. Medullary pyramids (A) are densely and abnormally echogenic, renal cortex (B) is normal

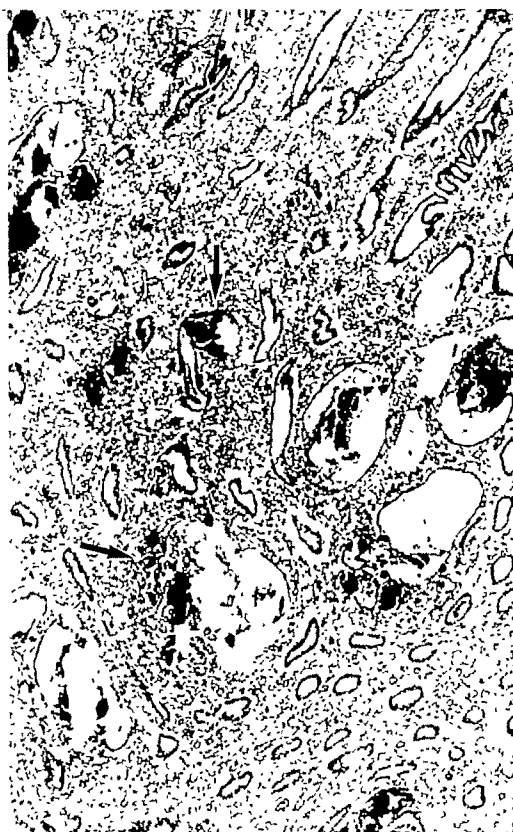


Fig 2 Photomicrograph of renal pyramid showing extensive nephrocalcinosis. Dense interstitial and intratubular calcium deposits (arrows) show staining and polarisation characteristics of mixed calcium oxalate and phosphate (Haematoxylin and eosin.)

enlarged and diffusely echogenic. Juvenile familial nephronophthisis may also show increased echo formation, particularly around the periphery of the medullary pyramids and associated with microcyst formation. Some larger cysts may also be visible.

Unlike Seyberth *et al* we found no abnormalities in tests of tubular function.⁴ Microscopic haematuria has been seen in infants with nephrocalcinosis who are given frusemide, but it does not seem to be associated specifically with nephrocalcinosis.

The combined use of chlorothiazide with frusemide has been advocated as a means of preventing hypercalcaemia. It also aids the dissolution of nephrocalcinosis and any stones that may be present.² We have shown that nephrocalcinosis can disappear without using chlorothiazide over a period of 16 months after stopping the frusemide. The most valuable use of chlorothiazide may be in those infants who have developed kidney stones² and in those with osteopenia of prematurity. The volume of fluid tolerated by the infant receiving frusemide seems to be important in the development of nephrocalcinosis.

The long term effects of medullary nephrocalcinosis are unknown, but may be related to the density of calcium present and the underlying cause. The absence of tubular abnormalities in our group at 12

months suggests that they did not have any ill effects.

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Ranitidine in the newborn

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SUMMARY An infusion of ranitidine 0.2 mg/kg/hour abruptly halted a life threatening gastrointestinal haemorrhage in an anuric infant of 30 weeks' gestation.

We report the successful use of intravenous ranitidine in an extremely sick preterm neonate with severe acute gastrointestinal blood loss.

She was born at 30 weeks' gestation with a birth weight of 1700 g to a healthy primigravida. She required brief initial resuscitation with endotracheal intubation and assisted ventilation in addition to naloxone. Vitamin K was given intramuscularly. The infant developed respiratory distress and collapsed when 5 hours old with a generalised convulsion that required further intubation and assisted ventilation. She remained hypoxic despite vigorous ventilation,

with the fractional inspired oxygen concentration being raised to 95%, and persistent fetal circulation was diagnosed. A bolus dose of tolazoline 2 mg/kg was given followed by an infusion at 2 mg/kg/hour, which produced a good initial response. She was transferred to the regional neonatal intensive care unit at the age of 12 hours.

Chest x ray pictures showed severe hyaline membrane disease and the baby continued to shunt with a PaO_2 of only 5.33 kPa despite ventilation with 95% oxygen and infusions of tolazoline and dopamine (5 $\mu\text{g/kg/minute}$). At 40 hours of age she developed a loud murmur consistent with a persistent ductus arteriosus; this responded within nine hours to indomethacin 0.2 mg/kg and three doses were given 12 hourly intravenously.

On the third day she became anuric; renal ultrasound scan suggested acute tubular necrosis, and she required peritoneal dialysis for 36 hours for

Table Concentrations of ranitidine in plasma and urine

Time	Ranitidine concentrations		
	Plasma (ng/ml)	Urine (ng/ml)	Serum creatinine concentration (mmol/l)
After 24 hours of infusion	789	Not done	197
After 36 hours of infusion	Not done	11 520	139
7 Hours after end of infusion	1390	Not done	100
24 Hours after end of infusion	Not done	21 480	Not done
36 Hours after end of infusion	375	Not done	Not done
48 Hours after end of infusion	Not done	2276	116

Plasma level which results in acid suppression in 50% of adults=100 ng/ml

fluid retention and a serum potassium concentration of 8.6 mmol/l. She developed ventricular tachycardia which did not respond to lignocaine given intravenously but reverted to sinus rhythm after a direct current shock of five joules.

At 96 hours of age, she had an acute gastrointestinal bleed indicated by a single aspirate of 28 ml of fresh blood from her nasogastric tube followed by a further 41 ml over the next seven hours. There was no clinical suggestion of a generalised bleeding disorder, though clotting studies were not performed. Her platelet count was $304 \times 10^9/l$. She was initially treated conservatively with blood transfusions and alkalis given orally but because of the severity of the bleeding (equivalent to 50% of total blood volume), ranitidine was given intravenously, 0.2 mg/kg/hour for 37 hours. The bleeding stopped within two hours and only 2 ml of blood were aspirated during the following 24 hours. The table shows the serum and urinary concentrations of ranitidine that were monitored for the next three days.

The infant was extubated on the ninth day and sent back to the referring hospital on day 20 taking a normal diet. At the age of 5 months she was well and developing normally.

Discussion

There have been few reports of the use of histamine H_2 receptor antagonists in preterm neonates. Although the successful use of cimetidine (4 mg/kg 12 hourly intravenously) has been reported in a preterm neonate with gastrointestinal bleeding and

a creatinine of 20 mg/dl,¹ ranitidine was chosen for the anuric neonate reported here because a greater proportion of ranitidine than cimetidine is excreted through the liver^{2,3} and because of the possibility of cerebral toxicity induced by cimetidine.⁴

The ranitidine infusion controlled the gastrointestinal haemorrhage within two hours, the likely cause of which was the combination of tolazoline and indomethacin treatment.

Ranitidine reduces gastric acid secretion by histamine H_2 antagonism. Release of histamine is thought to be both the mechanism of action of tolazoline in treating pulmonary hypertension and the cause of the gastrointestinal bleeding that complicates tolazoline treatment.⁵ Such bleeding has been reported in up to 55% of neonates receiving tolazoline and 7% were severely affected.⁵ The theoretical risk of histamine antagonism by ranitidine leading to a recurrence of pulmonary hypertension was possible, but did not develop.

Extracranial haemorrhage has been reported in 22% of neonates given indomethacin for persistent ductus arteriosus.⁶ This may be due either to a prolongation of the bleeding time, which is still considerably increased 48 hours after course of indomethacin treatment, or to a direct effect on the stomach, or both.

Our patient had a high plasma concentration of ranitidine at 24 hours and it accumulated thereafter. The infusion of 0.2 mg/kg/hour was effective though excessive in treating life threatening haemorrhage in an anuric preterm infant.

We thank Dr DG Sims for allowing us to report this patient and Glaxo PLC for measuring ranitidine concentrations in serum and urine

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Current topic

Maternal depression and impact on children's development

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The association between mental disorder in parents and abnormalities in their children's development is well established. It is strongest when parents have a personality disorder, or a chronic or recurrent depression, or emotional disturbance, and possibly somewhat less if they have schizophrenia.¹ In the community depressive disorders are widespread with prevalence for non-bipolar depression in women ranging from 4-9%.² Prevalence rises to 25% among mothers in urban populations with children of school age³ and to 40% among metropolitan working class mothers with young children.^{4,5} Puerperal psychoses and postnatal depression may be of particular importance because of the possible effect on the early development of the relationship between mother and child. Puerperal psychoses are rare⁶ but the onset of neurotic depression is particularly common in the three months after delivery; a new episode occurring in 10-15% of women.⁷ It may also occur more often in the first trimester of pregnancy.⁷

If maternal depression does have an important adverse effect on children's development, it is a major health issue. There are, however, reasons to think that the association between maternal depression and various indices of disturbed development in children are not a straightforward consequence of the child's exposure to depressive symptoms.

Strength of the association between maternal depression and child psychiatric disorder

When a mother is depressed, the rates of psychiatric disturbance in the children are commonly reported as between 50 and 50% whatever the age of the child.⁸⁻¹¹ In at least one study much lower rates (12% according to the mother) have been recorded,¹² but in all cases, rates of disorder in the children of depressed mothers are usually two or three times those found among normal control mothers.

Assessing the association is complicated not only

by the age of the child at evaluation, but by what measures are used, the criteria for diagnoses in the parents and children, the timing of the onset of the parental disorder,¹³ and the source of information about the child—for example, depressed mothers may over report a child's symptoms.^{12,14} The term depression also covers a wide variety of other disorders. The Yale Family Study of Major Depressive Disorders distinguished types of parental depression according to their association with different types of anxiety disorder and found rates of child disturbance varying from 15-42% according to parental diagnosis.¹⁰ Parental diagnoses were lifetime diagnoses, but child diagnoses were current, and in the study parents were both male and female 'primary unipolar depressives'. Beardslee *et al.*, were unable to separate rates of disorder in the children of parents with bipolar as opposed to unipolar disorders because of the methodological differences between studies, and because of the young age of some parents reported as 'unipolar' who might have developed a bipolar illness later in life.⁸ The only study clearly distinguishing between the two types of depression found higher rates of psychiatric disorder in the offspring of parents with unipolar depression compared with those with bipolar depression.¹⁵ The annual incidence of unipolar depression, however, is about 500 times that of bipolar depression so that bipolar depression has considerably less impact on children from a public health point of view.²

The nature of the association between maternal depression and child psychiatric disorder

GENETIC CONTRIBUTIONS

Studies distinguishing different types of depression may be concerned with elucidating genetic influences from one generation to another and these could provide one explanation for the association between maternal depression and psychiatric disturbance in children. When offspring of adults with different types of adult mental disorder are com-

pared, however, the child's disorder does not usually match that of the parent in a systematic way and this argument has been used against a genetic mechanism.¹ Recent interest in depressive disorders in children¹⁶ has led to increasing awareness that the importance of depressive symptoms in children may have been overlooked¹⁷ and depressive symptoms often continue from childhood to adult life.¹⁸ There may therefore be more similarity in depressive symptomatology between adults and children than has previously been reported. Two recent studies of major depressive disorders support this view, although one included bipolar depression and the other did not.^{10, 19} The finding does not necessarily indicate a genetic basis for the similarity and indeed dissimilarity does not preclude such a basis because signs of a disorder in childhood could differ from those in adult life. For disturbances in childhood, however, relevant genetic studies are lacking, so it is not possible to do more than speculate about the way in which genetic and environmental influences interact. Although a genetic factor has been shown in the aetiology of most of the major psychiatric illnesses of adults, it is possibly less important for the broad range of affective disorders seen in the community,¹⁹ even though such disorders may be no less severe than those seen in psychiatric hospital.²⁰

EXPOSURE TO SYMPTOMS

How do the non-genetic influences operate? There may be a direct effect of maternal depressive symptoms, which is more pronounced if they involve the child.²¹ Maternal depression may have a specific influence on child development in this way. Several symptoms which commonly occur in depression, however, such as loss of appetite, irritability, crying, poor concentration, and lack of energy are not peculiar to depressive disorders. This is also true of suicidal ideation and behaviour. Expressions of worthlessness, hopelessness, and loss of pleasure are perhaps more specific to depression but they are seen at least sporadically in people who are not depressed. What may be important is not whether a parent is depressed but how they express it. This is what the child experiences and it may be more associated with the personality characteristics of the parent than the presence or absence of depression. Although there are a number of observational studies of depressed women and their children, they have not been concerned with this specific issue but rather have looked at whether there are characteristic changes in the quality of parental care

CHANGES IN THE QUALITY OF PARENTAL CARE

It is useful to distinguish between exposure to symptoms and changes in parental care.²² A parent

may involve a child in a depressive delusion, in which case the child is exposed to the symptom in a way that also constitutes a change in the quality of care. Alternatively, the parent may be preoccupied with the delusion and thus be less responsive to the child. There is then no direct exposure to the symptom, but there is change in the quality of care; these changes are not peculiar to depression, although the former type may be

Weissman *et al* list various impairments of maternal care resulting from depression which might show themselves at different stages of the child's development; in infancy, for example, the mother might show helplessness, overindulgence, or hostility, excessive concern, and inability to separate from the child and, in adolescence, impaired communication, friction or withdrawal, resentment, worry, guilt, envy, and competition.²³ It is obvious that these impairments, if they exist, cannot be specific to depression.

Observational studies are now beginning to map interactions between parents and children when the mother is depressed to establish whether there are characteristic changes in care among depressed mothers. These studies have predominantly focused on infants and children under 5 years (L Murray, personal communication).^{22, 24-26}

The interactions of depressed mothers and their infants are characterised by the mothers being less active, decisive, and responsive^{25, 27} with less well timed responsiveness (L Murray, personal communication), and lower levels of warm acceptance of the child.²⁸ The infants are more drowsy, less content, more distressed and fussy,²⁵ look at their mothers less and engage in more self directed activity (L Murray, personal communication).²⁴

In comparison with mothers who are not depressed, the depressed mothers of 2 year olds have less well timed responsiveness, express more negative attitudes, ignore the child's approaches more, and use more control talk or action. They also use less elaborate talk with their children—for example, explanations, suggestions, and questions.²² The 2 year old children are more sensitive to emotional distress, reacting with avoidance or 'exceptional compassion' (Radke-Yarrow *et al*, personal communication), and often comforting their unhappy parents.²² They approach their mothers verbally less often, but physically more often, and more frequently show signs of emotional or behavioural disturbance (M Radke-Yarrow *et al*, personal communication).²² The interactions of depressed mothers are more frequently punctuated by distress of the child, and the mother using controlling methods in the face of this.²² Children of depressed mothers need to make more intense demands to get

a response, and their mothers are then more often indecisive, finally capitulating: a pattern of child 'coercion-control'.²²

These studies have only compared children of depressed mothers with those of non-depressed mothers, however, so that the difference in interactions between parent and child cannot be said to be specific for depression; in one study there was a wide range of quality of interactions between parents and children, especially among the depressed group.²² Some depressed mothers were as sensitive and skilful as those in the control group—some more so. Similar observational methods were used in a study of children who failed to thrive and their parents. Differences in the quality of parental care in the group of depressed parents and those whose children failed to thrive overlapped in—for example, less well-matched responsiveness, greater expressions of negative affect, and ineffective control (C Pucsering, personal communication). Families of children who failed to thrive tended to be more chaotic and mealtimes were particularly so, with the mothers unconcerned or overinvolved.²⁸ There is clearly overlap in the nature of the interaction between parents and children with some families who abuse their children,²⁹ although in these the dysfunction in interaction is more evident in discipline and control. A prospective high risk study of women with histories of psychosis—schizophrenic, cycloid, or affective—found no deviant aspect of the interaction between mother and child which consistently characterised any given diagnostic group when the children were aged 1.²⁷ It must be emphasised that the results obtained by observational methods will depend largely on the focus of investigation and what behaviour patterns are recorded.

Fairly characteristic patterns of interaction will be found in some families who have specific defining characteristics, such as maternal depression. Extreme forms of such characteristics may be seen as pathognomonic but will be shown by only a proportion of families with that particular characteristic.

CORRELATED FACTORS, INCLUDING CHANGES IN FAMILY STRUCTURE OR FUNCTION

The demonstration that some depressed mothers behave differently with their children does not indicate that the differences are necessarily due to depression, and the finding that not all depressed mothers differ from non-depressed mothers suggests that the basis for the differences may originate somewhere other than in the mother's depressed mental state. The depressed mother's mental state may affect the severity of any deficiencies in parental care or even the pattern in susceptible

individuals. In their study of depressed mothers of 2 year olds, Cox *et al* found that depressed mothers differed from the control (non-depressed) mothers both in their backgrounds and in their current circumstances.²² Depressed mothers more often reported a poor relationship with their own mothers during childhood, and frequently played truant from school. They had given birth to their first child at a younger age than mothers in the non-depressed group. All these experiences are likely to reduce confidence and possibly competence in parental care. At the time of the study depressed mothers were more often living in threatening environmental circumstances, and having discordant relationships with their partners. In addition, their children had more problems in relationships with siblings, peers and the mother herself. Furthermore, the spouse more often had a psychiatric disorder. All these factors might have a bearing on the quality of the relationship between parent and child.

A recent study of an older group of children and their mothers showed that the mothers were appreciably more aversive to the children on days when they themselves experienced a high proportion of unpleasant contacts with adults.³⁰ Similar findings were reported in a study of mothers with preschool children, although in this study, the authors argued that the child's behaviour was the best single predictor of the mother's response, followed by maternal depression, and then 'mother coercive interaction with adults'.³¹

There are clearly many possible mechanisms. For example, mothers with poor experiences in early life may be prone to both depression and to poor parental care. Mothers subjected to a lot of stress may as a result be unpleasant to their children as well as depressed. Longitudinal studies are needed to clarify the various patterns.

FINDINGS FROM LONGITUDINAL STUDIES

In their follow up study comparing a group of children with disturbed behaviour and a random control group of children from the age of 3 to the age of 8, Richman *et al* found that maternal criticism and lack of warmth were better predictors of the onset or persistence of disturbed behaviour in the child than maternal depression and marital discord, although the two latter factors correlated with disturbance at the different ages when the children were studied—namely, 3, 4, and 8 years. Maternal depression when the child was 3, however, was the best predictor of later educational difficulties at the age of 8, independent of the child's intelligence quotient.⁵

In a report of a four year prospective study of children one of whose parents had attended a

psychiatric clinic, Rutter *et al* found that personality disorder in the parent and exposure of the child to high degrees of hostility were the best predictors of persistent psychiatric disorder in the child. Parental mental disorder was one of several adverse psychosocial factors which were associated with psychiatric disorder in the children in varying combinations, and which tended to aggregate. After allowing for the other factors, parental mental disorder was not associated with increased rates of child psychiatric disorder in the children. A recent evaluation of a group programme also reported behaviour disorders in children as being linked to the mother's outwardly directed irritability rather than her depression.³²

Further useful evidence about mechanisms comes from three longitudinal studies in which mothers were followed up from pregnancy or parturition until the children were 3 or 4 years old (NH Caplan *et al*, personal communication).^{9 33-35} In most instances the behavioural disturbance in the child was most strongly associated with concurrent depression. In a complex analysis, Ghodsian *et al* show that at the age of 42 months the child's psychiatric disturbance was not associated with maternal depression four months after birth, but was associated with maternal depression when the child was 14 months old.³⁴ Investigating the children when they were 3 years old, Wrate *et al* also found no link between psychiatric disturbance in the child and postnatal depression present three to five months after birth.³⁵ Mothers with shorter postnatal episodes, however, had children with more behavioural disturbances at the age of 3 (but most of them had had a subsequent depression sometimes following a further pregnancy). The third study (NH Caplan *et al*, personal communication) was of a group from a higher class than the previous two studies.³³ They found that maternal depression at some time in the first year after delivery was associated with the children having lower scores on the McCarthy scales of children's abilities at the age of 4. Lower scores were independently linked to marital conflict and a history of paternal psychiatric problems. Behavioural disturbances in the 4 year old children were associated with lower scores on the McCarthy scales. Such disturbances were linked more strongly with current as opposed to past depression, with a paternal history of psychiatric disorder, and current marital discord. Discord had usually been persistent from before the delivery.

Discussion

How are these findings to be interpreted?

Firstly it seems that early severe maternal post-

natal depression does not carry a seriously increased risk for later psychiatric problems in children, although episodes of depression during the first year of life may be important in the child's later cognitive and language development. Secondly, current child behavioural disturbance always correlates best with current maternal depression. Thirdly, there are many important factors which are associated with both psychiatric disorders in children and maternal depression.

The positive findings are best understood by considering the quality of the relationship that develops between the mother and child, bearing in mind that aspects of the relationship relevant to cognitive or language development may be different from those relevant to the development of psychiatric disorders in childhood. The features of the relationship relevant to personality development that might make an individual susceptible to depression as an adult may be different yet again.

What is suggested is that patterns of mutual responsiveness between mother and child that may be particularly relevant to the development of cognitive abilities, attention, and language develop in the first two years of life and that these are particularly at risk if there is maternal depression. There is support for this in the finding that poor mutual responsiveness between mother and child when the child is 2 years old is associated with poorer expressive language.³⁶ If the findings of Cogill *et al* are substantiated, the basis for this deficiency is established in the first year.³³ It must still be said, however, that it is not clear whether depression as such is responsible for the unsatisfactory mother and child relationship. The sample studied by Cox *et al* was followed up after six months when the children were about 3 years old.²² Looking at the pattern of correlations at and between the two different time points, mutual responsiveness between mother and child is more closely linked to the quality of the mother's marriage than to the severity of her depression. Depression and the quality of marriage influence each other.²² It therefore seems likely that the mother's mental state, the quality of her marriage and social supports, and her personality all contribute to the establishment of a relationship between parent and child that is deficient in responsiveness, and which in turn adversely affects language (and possibly cognitive) development. These deficiencies in language development then provide the basis for later educational failure.⁵

Other patterns of the relationship between mother and child occurring in association with maternal depression may be particularly relevant to the development and persistence of psychiatric disturbance in the child. Adverse patterns that may

be predisposed to by delayed cognitive and language development will become established when the child starts to be more mobile at or around 14 months, and may be especially likely to occur if a sibling is born about this time.²⁴ The pattern centres around child control: excessive use of controlling techniques, exposure to hostility, and a pattern of child coercion control in which the child increases the pressure until he or she gets what they want. This pattern will be more likely to develop if the mother is subject to stressful and unpleasant contacts with others²⁹ especially marital problems.² Once the pattern has developed it will persist even when distress or depression have diminished.^{11, 22} Maternal depression is closely linked with marital difficulty, and may exacerbate or intensify the maladaptive patterns of interaction between parent and child.^{19, 37} It is doubtful, however, whether it is sufficient on its own as a cause, because so many depressed women do not develop such a pattern if there is no concurrent marital discord.

The types of disturbance in children that are due to exposure to hostility predominantly affect their conduct.¹⁵ It is therefore reasonable to consider that there may be modes of interaction between parent and child more specifically linked to maternal depressive mental states; these produce less immediate disturbance in the child but generate a vulnerability to emotional disorder in later childhood or adult life. Radke-Yarrow *et al* have described the variety of patterns of attachment in 2 year olds according to the mother's history of different types of depression.²⁶ In a follow up study of children aged between 1 and 6 years, Lewis *et al* found that patterns of attachment at one year were significantly related to later psychopathology for males but not females.³⁵ One possibility is that it is girls in particular who develop anxious attachment to their mothers which entails a role reversal so that the child takes an undue or predominant part in ministering to the mother's emotional needs; in childhood this would not be construed as a psychiatric disorder. It has been suggested, however, that children subject to such role reversal may lack security in later life and be prone to depression and difficulties with relationships.³⁹

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Personal views

Medical staffing in paediatric departments in district general hospitals

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The present situation

In 1978 the Manpower Economic Review established by the Doctors and Dentists Review Body identified paediatricians as one of the hardest working groups of consultants with the highest rate of recall back to hospital out of hours. Now, nine years later, the situation has deteriorated considerably because the workload within many paediatric departments has continued to increase without any significant improvement in medical staff levels. This increase in workload includes inpatient admissions, the increasing intensity of neonatal care, and the greater recognition of physical and sexual abuse of children. Figures published by Her Majesty's Stationery Office show that deaths and discharges for paediatric units in England and Wales increased by 42.5% during the 11 years, 1974-1984.¹ During the same period the increases for general medicine and for general surgery were 21% and 2.7%, respectively. There has been no significant change in birth rate over recent years but the intensity of care provided by neonatal departments is continuing to increase at a tremendous rate. For example, in the Northern Region during 1978, 50 newborn infants received assisted ventilation. By 1983 the number had increased to 375, an increase of 650%.

Hospital inpatient paediatrics and neonatal care is undoubtedly an acute specialty. It should therefore have adequate levels of consultants and experienced junior medical staff to provide an adequate and safe service. In many districts this is clearly not so. For example, within the Northern Region eight out of 15 health districts have no established registrar posts within their paediatric department. Junior medical staff cover is therefore almost totally provided by senior house officers who have no previous postgraduate experience of paediatrics and particularly of neonatology. Many of these doctors are training for careers in general practice where experience in hospital neonatal care is largely irrelevant.

Within these same districts comparison with other specialties can show dramatic differences. For example, within my own district, Gateshead, the paediatric department has an established medical staff of 2.7 consultants and three senior house officers, all with no previous postgraduate paediatric experience. The combined general and geriatric medical unit has six consultants, four registrars, and 10 experienced senior house officers, and the general surgical unit has four consultants, three registrars, and four senior house officers who have had previous surgical experience. The paediatric unit is the only clinical and non-clinical unit in the district that has no established registrar cover.

Opportunities for change

During the past 15 or more years it has been virtually impossible to establish new registrar posts in paediatrics. The present situation is therefore in part a legacy of former consultant paediatric colleagues who failed to achieve adequate junior medical staff levels in paediatric departments when opportunities for expansion were possible. I believe that opportunities for change may occur in the near future and that paediatricians should now make a unified, concerted effort to publicise the present disgraceful level of medical staffing in many district general hospital paediatric departments.

Achieving a balance²

An important objective of the 'achieving a balance' exercise is clearly to try and reduce the tremendous bottleneck that has developed at registrar and senior registrar levels in some specialties. This is not a major problem in paediatrics and therefore although paediatrics is undoubtedly an acute specialty, it was specifically excluded from the limited consultant expansion programme that is funded centrally. Training in hospital paediatrics is relevant for future

general practitioners and for consultants in community as well as hospital paediatrics. Despite the present financial constraints significant expansion of consultant community paediatric posts is likely to continue, funded by individual districts from revenue released by retirement of senior clinical medical officers etc. It is reasonable to argue therefore, that a limited expansion of junior medical posts in paediatrics may be possible without seriously jeopardising the career prospects of paediatric registrars and senior registrars.

If the medical staff levels within paediatric departments in the Northern Region are similar to those of other parts of the country then it will require an enormous increase in the number of registrar and senior house officer posts to implement two important recommendations of the 'achieving a balance' document. They are firstly, that most acute specialties in each district should have at least one regional registrar, and secondly, that there should be a minimum level of 24 hour cover, the so called 'safety net.' If the proposals of this document are achieved then there may be some redistribution of junior medical posts between different specialties. A strong case for improvements in the medical staffing of paediatric departments needs to be made now at national, regional, and district level.

Joint Planning Advisory Committee

The Joint Planning Advisory Committee (JPAC) is at present reviewing the distribution of senior registrar and registrar posts between different regions. To date the situation in paediatrics has not been investigated. From my position in Gateshead I await the deliberations of this committee related to paediatrics with great interest. The Northern Region has already acquired manpower clearance but unfortunately not the revenue to establish 19 additional senior registrar posts in specialties which include orthopaedics, psychiatry, clinical genetics, etc. The Northern Region expects to receive manpower clearance to establish more senior registrar posts as the JPAC exercise continues and other specialties, including paediatrics, are considered. This is clearly an opportunity to improve the junior

medical staff cover of districts which are particularly poorly served at present.

The response of the British Paediatric Association

When I read the paper *Hospital medical staffing*³ outlining the British Paediatric Association's response to the consultative document, *Hospital Medical Staffing—Achieving a Balance*, I was dismayed at the bland response. Surely this is an opportunity for the Association to make a strong statement to the government on behalf of paediatrics and the hospital services provided for children in Britain. My own experience indicates that the medical cover for paediatric departments, and particularly for neonatal care in this country, is at present a disgrace for an allegedly civilised, developed nation. If the situation in Gateshead is typical of a significant number of other districts then clearly members of the British Paediatric Association Council and senior paediatricians are out of touch with conditions in many paediatric units.

In September we were asked to vote on the important question 'Should the BPA become a separate college or a faculty of the Royal College of Physicians?' One of the main arguments for change was the widely held view that the case for child health and for the medical needs for children needs to be voiced more strongly. The document 'Achieving a Balance' provides the Association with an opportunity to pronounce upon an important aspect of child health in this country—that is, the medical staff levels within hospital departments. If the present response is an example of the Association's attempts to improve the child health services in this country then I believe that September's vote was irrelevant.

References

- ¹ Anonymous *Health and personal social services statistics for England* London HMSO, 1986,74-5
- ² DHSS/JCC Manpower Initiative 'Hospital Medical Staffing—Achieving a Balance,' *Br Med J* 1986,293:147-51
- ³ Jackson ADM Hospital medical staffing *Arch Dis Child* 1987,62:872

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Medical and nurse staffing for newborn care

P M DUNN

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In the July issue three distinguished neonatal nurses, P Hale, J Boxall, and M Hunt, explored the suggestion that has been made, and discussed in an Annotation,¹ that the current shortage of junior medical staff in neonatal intensive care units might be solved by the creation of a new grade of neonatal nurse practitioners with clinical skills and responsibilities. In their letter they pointed out the fact that the shortfall in neonatal nurses is just as great as that for doctors and the authors warned that the introduction of this new role was likely to create many problems in terms of training, financing, in lines of command, and so on. They urged great caution and careful study to ensure that the present unsatisfactory level of newborn care was not further compromised. I agree with them. We should first examine the reasons for the present situation and attempt to put them right.

Neonatal intensive care developed in the United Kingdom in the 1970s against a background of steadily increasing financial difficulty. In one sense the development created its own problems in that babies that had previously been stillborn or had died soon after birth were now delivered alive and survived, often after weeks or months of intensive care. In my own hospital the perinatal mortality fell between 1968 and 1985 from 46 to seven deaths per 1000 births. The Sheldon report² estimated a need for 0.5 intensive care cots per 1000 deliveries per year in 1971; by 1978 this requirement had doubled. Since that time the greatly improved prognosis of very early babies has increased the need to its present level of 1.5 cots per 1000 deliveries in 1987. Hopefully, now that neonatal care has reached down to the lower limits of viability (22-24 weeks' gestation) this represents the near maximum demand likely to be made for further resources.

At the time of the Sheldon report there were practically no facilities for neonatal intensive care in this country. In the ensuing years progress has been slow because of the economic climate and only very recently have the 1971 recommendations been broadly implemented. In the meantime the workload has tripled and the need for increased staffing and facilities remains as acute as ever. The impact of

an unsustainable workload and the stress it engenders has fallen particularly heavily on the nursing staff and has predictably led to a recruitment problem, thus creating a vicious circle. The situation is very serious and must be tackled at once if the service is not to founder. Care of the newborn should be very attractive to nurses. That this is not so underlies the astonishing shortsightedness of those responsible for the present state of affairs whether in government, in NHS management, or in the hierarchy of the nursing profession.

What can be done? First and foremost, every neonatal intensive care unit should have the appropriate number of intensive care cots and the minimum nursing establishment of four nurses per cot to go with them.³ Second, there should be a major expansion in neonatal training courses and the provision of funds to enable nurses to be seconded to them. Third, the talents, experience, and responsibilities carried by senior neonatal nurses should be recognised in terms of added remuneration and also in career prospects within a clinical setting. Fourth, skilled nurses should be relieved of the non-nursing duties that they often have to undertake, such as acting as ward clerks and receptionists. Fifth, each neonatal intensive care unit should examine ways of making working conditions more attractive and less onerous—for example, by improving rest facilities, rotating nurses between the unit and the transitional care nursery or postnatal wards, improving inservice training and, where appropriate, increasing the nurse's technical responsibilities in the care of the baby.

The situation regarding medical staffing is as serious as that for neonatal nursing. Although a steady expansion has taken place over the last 15 years, it has not kept pace with the growth of the service. Furthermore, for reasons of economic expediency, there has been an imbalance in the expansion favouring the creation of resident junior doctors rather than the more expensive non-resident consultant staff. Thus, in Bristol with two major maternity units catering for 11 000 births each year and providing a regional neonatal referral service, there are 12 whole time paediatric residents and just

two consultant whole time equivalents. Now manpower and training considerations require that the shape of this pyramid be changed and, indeed, be turned upside down. Any attempt, however, to reduce the number of junior residents without first greatly expanding the senior staff would have a catastrophic effect. In countries with consultant led neonatal services (including resident duties) it is usual to have roughly one consultant per 1000 deliveries per year. In the United Kingdom this would require a five to six fold increase in neonatal consultant posts. Needless to say this would be very expensive. Such an expansion, however, would at the same time go some way towards justifying the training of the present number of junior neonatal doctors. Further scope for compromise would be possible if those shaping our manpower needs came to appreciate that neonatal posts, and especially when these are combined with obstetrics in the district general hospital, provide ideal professional training for doctors seeking careers in general practice and community medicine. With most babies

returning home within two to three days of delivery a sound knowledge of the newborn is essential to the primary health team. The relatively small number of posts required to staff regional neonatal intensive care units might then be, for the most part, reserved for doctors training for careers in paediatrics, perinatal medicine, or obstetrics.

References

- ¹ Chiswick ML, Robertson NC Doctors and nurses in neonatal intensive care. towards integration *Arch Dis Child* 1987;62:653-5.
- ² Report of the expert group on special care for babies *Reports on Public Health and Medical Subjects* 1971,127 London: HMSO. (Sheldon report)
- ³ Midwife and Nurse Staffing and Training for Special Care and Intensive Care of the Newborn A consultative document prepared by the Standing Joint Committee of the British Paediatric Association/Royal College of Obstetricians and Gynaecologists, 1983:1-11

Correspondence to Professor PM Dunn, University of Bristol Department of Child Health, Southmead Hospital, Bristol BS10 5NB

Meetings in 1988

Neonatal Society

18 February, London

8-9 July, Leicester

3 November, London

Further details: Dr JK Smeeths, Neonatal Research Unit, London Hospital Medical College, Turner Street London E1 2AD

Paediatric Research Society

18-19 March, Girton College, Cambridge

Further details: Dr A Greenough, Neonatal Unit, King's College Hospital, Denmark Hill, London SE5 8RS

XI European Congress of Perinatal Medicine

10-13 April, Rome

Further details: Dr GC Di Renzo, Scientific Secretariat, via degli Olivi, 72, 06100 Perugia, Italy

British Paediatric Association

12-15 April, York, England

Further details: Miss RJ Topping, Conference Secretary, British Paediatric Association, 5 St Andrew's Place, Regent's Park, London NW1 4LB

Clinical Genetics Society

13-14 April, Oxford

22-23 September, Aberdeen

Further details: Professor NC Nevin, Dept of Medical Genetics, Floor A, Tower, Belfast City Hospital, Northern Ireland

American Pediatric Society

2-6 May, Washington DC

Further details: M Benedict, Suny Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 49, Brooklyn, New York 11203

Fetal and Neonatal Physiological Measurements

5-8 June, Malmö/Kornäby Brunn, Sweden

Further details: M Fickens, Dept of Clinical Physiology, Lund University, Allmänna Sjukhuset, S-214 01 Malmö, Sweden

European Society for Pediatric Research

15-22 June, Oslo

Further details: Professor S Halvorsen, Dept of Pediatrics, Oslo City Hospital U1 Uvel, Kirkevein 166, N-Oslo 1, Norway

European Society for Paediatric Endocrinology

26-29 June, Copenhagen

Further details: Dr NE Skakkebaek, University Dept of Paediatrics, Dept of Paediatrics 531, Hvidovre Hospital, Kettegaard Alle 30, DK-2650 Hvidovre, Denmark

International Association for the Scientific Study of Mental Deficiency

21-25 August, Dublin

Further details: Mr J O'Gorman, Congress Chairman, 8th World Congress, IASSMD, 12 Pembroke Park, Dublin 4, Ireland

III International Symposium on Pediatric Dermatology

14-17 September, Mazara del Vallo (Trapani), Italy

Further details: Organising Secretariat, Foundation for Research in Dermatology, Largo Gemelli, 3, 00168 Rome, Italy

International Society for the Prevention of Child Abuse and Neglect

25-28 September, Rio de Janeiro

Further details: Dr MA Lynch, Newcomen Centre, Guy's Hospital, St Thomas Street, London SE1 9RT

European Paediatric Respiratory Society

No meeting in 1988 (alternate years)

Further details: Dr J Warner, Brompton Hospital, Fulham Road, London SW3 6HP

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Submission of a paper will be held to imply that it contains original work not being offered elsewhere or published previously.

Manuscripts should be prepared in accordance with the Vancouver style.¹

The Editors retain the right to shorten the article or make changes to conform with style and to improve clarity.

For guidance on ethical aspects refer to the editorial in this journal.²

All authors must sign the copyright form.

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Original articles

These should usually conform to the conventional structure of summary, introduction, patients and methods, results, discussion, and references. The title should occupy no more than two lines of the title page (eight to 10 words) and should not contain the words 'child', 'children', or 'childhood' (already implicit in the title of the journal). The summary should be no longer than 150 words and should set out what was done, the main findings, and their implications. 'Results will be discussed' is not acceptable.

Short reports

Short papers, brief laboratory observations, and preliminary communications should be submitted for this section (single case reports will usually be considered in this form only). Length must not exceed two printed pages of text. In general this will be less than 900 words, including a summary of less than 50 words, one or two small tables or illustrations, and up to six references. An abbreviated title of no more than 38 characters is required for the title page. A report of a trial with negative results, based on a reasonable hypothesis, is more likely to gain acceptance if submitted as a very short report of less than 500 words.

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Annotations are commissioned by the editors who welcome suggestions for topics or authors.

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Letters should normally be no more than 300 words, have no more than three references, and be signed by all authors. Letters may be published in a shortened form at the discretion of the Editor. They should be prepared in a similar way to other manuscripts. Preference is given to those that take up points made in contributions published in the *Archives*, but those that discuss current topics or present original observations may be acceptable.

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Drugs should be given their approved, not proprietary names, and the source of any new or experimental preparations should be given. Abbreviations should not be used. Scientific measurements should be given in SI units: conversion factors to traditional units should also be supplied. Blood pressure, however, should be expressed in mm Hg.

All statistical methods used should be detailed in the 'methods' section of the paper and any not in common use should either be described in detail or supported by references. Previously published procedures and techniques need only a reference to the original.

Tables and illustrations should be submitted separately from the text of the paper, and legends to illustrations should also be typed on a separate sheet. Tables should be typed in double spacing without ruled lines, be simple, and should not duplicate information given in the text of the article; they should be numbered consecutively and be comprehensible to the reader without the text.

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References

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ences and many need substantially less. References should be numbered in the order in which they appear in the text, and typed in double spacing. At the end of the article the full list of references should give the names and initials of all authors (unless there are more than six when only the first three should be given, followed by *et al*). The authors' names are followed by the title of the article, the title of the journal abbreviated according to the style of *Index Medicus* (see the January issue of *Index Medicus*), the year of publication, the volume number, and the first and last page numbers. Titles of books should be followed by place of publication, publisher, year, and page numbers of chapter if applicable.

¹ Barson AJ, Tasker, M, Lieberman BA, Hillier VF. Impact of improved perinatal care on the causes of death. *Arch Dis Child* 1984;59: 199-206.

² Dowling S. *Health for a change*. London: Child Poverty Action Group, 1983.

Information from manuscripts not yet accepted or personal communications may be cited only in the text. References are not checked by us; authors must verify references against the original documents before submitting the article. Information from abstracts may not be cited in the references but can be noted in the text to attribute originality.

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References

¹ International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1982;284:1766-70.

² Anonymous. Research involving children—ethics, the law, and the climate of opinion [Editorial]. *Arch Dis Child* 1978;53: 441-2.

Correspondence

Doctors and nurses in neonatal intensive care

Sir,

Drs Chiswick and Robertson seem to propose a new deal for neonatal nurses, but are they not really hoping to maintain doctors in the hospital service in the lifestyle to which they have been accustomed?¹ The fact is that all acute hospital services, not only neonatal ones, demand 24 hour care by trained, and that means permanent, staff. The idea that the primary function of our hospitals is the training of doctors is out of date and should be put to rest. What other service or industry in this country discards many of its workers at the moment when they have been trained and could be of the greatest value? It is not unreasonable to suggest that the staffing structure of the great Victorian voluntary hospitals is not applicable to hospitals in the twenty first century.

Reference

- ¹ Chiswick ML, Robertson NC. Doctors and nurses in neonatal intensive care: towards integration. *Arch Dis Child* 1987;62: 653-5.

H J LIEBESCHUETZ
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Sir,

The case for allowing nurses to assume some of the duties of medical staff in the intensive care baby unit could be put in a less circumspect way than by Chiswick and Robertson though perhaps less tactfully.¹ The problem of requiring more junior staff in a medical specialty than there are consultant posts eventually available for them is not new. Indeed it could be said to be an old tradition of United Kingdom postgraduate medical training. If this, for whatever reason, is no longer acceptable, the work of junior medical staff will either have to be taken over by additional consultants or by appropriately trained nurses.

Increasing the numbers of consultants is an expensive solution, condemning medical staff to a lifetime of working unsocial hours, and is a recipe for intractable personal rivalries within any one unit. On the other hand the sheer joy of employing nurses to do the work of junior medical staff would be boundless. A dedicated career nurse in such a position would avoid all the hassle of retraining medical novices every six months. She would work all hours, have no ambitions to replace the consultant, and by definition of work roles, she could not do so anyway. And on top of all that it would actually cost less money. To argue in this

situation that the nurses' job would be more interesting is the kind of thing that gives male chauvinism a bad name.

Neonatal nurses could do worse than chat to their midwifery colleagues. Without the considerable practical skills and professional experience of midwives more obstetricians would have to be employed to spend their lives delivering babies at night, and daytime gynaecological practice would be under threat. Midwives have attained the level of practical indispensability that paediatricians would wish on their own senior nurses. Why then is there so much unrest among hospital midwives? And why so much talk of the days when they worked alone in people's homes?

Reference

- ¹ Chiswick ML, Robertson NC. Doctors and nurses in neonatal intensive care: towards integration. *Arch Dis Child* 1987;62: 653-5.

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Hospital medical staffing: achieving a balance

Sir,

Our fears about the future of women doctors in paediatrics were confirmed on reading the British Paediatric Association's response to the consultative document, *Hospital medical staffing: achieving a balance*. Despite the intake of female medical students having been around 50% for the last decade, there is still a disproportionately small number of women reaching senior posts in a specialty recognised as popular with female doctors. While welcoming an attempt to redress the now serious problem of hospital staffing and career structure, the proposed new non-training intermediate grade seems to offer indefinite routine and emergency work to help distribute the amount of time spent on call. Experience has shown that such posts lead to frustration and loss of commitment with a deterioration in standards. We recognise that such posts would be desirable for a few female doctors but as members of the Medical Women's Federation we thoroughly agree with their policy, which is to advise any doctor strongly against taking one of these positions, though it may appear attractive in the short term at a time of heavy domestic commitments. Adequate part time training opportunities in posts equal in quality to those filled by full time doctors would serve the needs of these women better and lead to a higher standard of care in hospitals. Later they would be able to make a

larger professional contribution in posts appropriate to their capabilities, and have a chance to influence departmental and hospital policies. At a time when specialist training is becoming more prolonged we see the increase in posts of senior house officer grade as giving us registrars by another name, and pushing the bottle-neck further down the career ladder.

If both foreign and British graduates are to be doing the same rotations, and if the posts are to be of equal quality, then the contracts must all be held at regional headquarters so that acceptable rotations can be organised. As a majority of registrars will eventually obtain consultant appointments in district general hospitals, we believe that it should be obligatory for all registrars to have at least two years' experience in such hospitals. Opportunities for overseas graduates to work in teaching hospitals should also be available.

Despite much time and thought having been given to the problem of hospital staffing in 1980-81, little progress had been made by 1985. What has happened since then that could not have been foreseen? We now have imposed on us an ill thought out, hasty, and short sighted solution in a struggling hospital service which remains unsympathetic to the requirements of flexibility that are now needed for 50% of medical school graduates, so that their full potential may be realised.

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Concern over safety of SAGM blood

Sir,

We read with interest the letter from Drs Robertson and Chiswick. We recently carried out an exchange transfusion in a neonate using 500 ml of partially packed SAGM blood. She was born at 38 weeks' gestation, weighed 3000 g at birth, and required an exchange transfusion for ABO group incompatibility when 19 hours old.

Before the transfusion the infant's total serum protein concentration was 58 g/l, and the serum albumin concentration was 36 g/l. These fell to 43 g/l and 28 g/l, respectively, immediately after the transfusion. By the following day the patient's total serum protein concentration was 52 g/l with a serum albumin concentration of 32 g/l. A coagulation screen immediately after the transfusion showed a prothrombin ratio of 1.3, a kaolin cephalin coagulation time of 39 seconds [control 38 seconds], and a prothrombin time of 22 seconds [control 19 seconds].

This infant tolerated a SAGM exchange transfusion with a temporary fall in plasma protein concentration and no disturbance of coagulation. Partially packed SAGM contains protein concentrations that are one third to one half of those of normal plasma. Though SAGM donor blood may be safe for use in exchange transfusions in the well term infant, further assessment is required in the ill low birthweight baby.

Reference

- Robertson NRC, Chiswick ML. Concern over safety of SAGM blood. *Arch Dis Child* 1987;62:638.

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Peptic ulceration: long term outcome

Sir,

Murphy *et al* reviewed 110 children with duodenal ulcers.¹ We are carrying out a long term follow up study of 36 children with peptic ulcers. The clinical features are similar but the long term outcome is different. The aim of our study, begun in 1982, was to determine endoscopically the healing rate after eight weeks of treatment with ranitidine, and the rate of relapse after stopping the drug. Endoscopy was repeated every six months or when symptoms recurred. For ethical reasons no placebo group was included.

The average number diagnosed annually was seven, the mean age at diagnosis was 9 years 7 months (range 18 months to 19 years), the male:female ratio was 1.8:1 and the mean duration of symptoms before diagnosis two years four months. There was a family history of peptic ulcer in 47%. The commonest symptoms were abdominal pain (91%), vomiting (47%), and bleeding (11%). The maximal acid output after pentagastrin stimulation was two standard deviations above normal in 66%. Of six patients with antral and prepyloric ulcers the maximal acid output was raised in five and normal in one, suggesting an identical pathogenetic factor.²

The table shows the sites of the ulcers, the rate of healing in 34 patients, and the rate of relapse in the 30 who were followed for more than a year. Though our series is smaller than that reported by Murphy *et al*, some of these preliminary data can be compared with his.

The main difference is in the rate of relapse (36% compared with 70%) and the length of time before relapse.

Table Features of peptic ulcers in 36 patients

Features of ulcers	No of boys (n=23)	No of girls (n=13)	Total No (n=36)
Site			
Duodenum	18	10	28
Antrum or prepyloric zone	5	3	8
No healing after eight weeks	22/23	10/11	32/34
No relapsed	9/21	2/9	11/30

(mean 17 months, range four months to three years, and only two who relapsed within the first year) We adopted different criteria from Murphy *et al* to assess the rate of relapse: in their study recurrence of symptoms was considered to be a relapse. In five of our patients symptoms recurred but endoscopy failed to show any ulcer and none had symptoms of relapse at endoscopy. No differences were found between those who relapsed and those who did not in family history, duration of symptoms, or gastric acidity

References

- ¹ Murphy MS, Eastham EJ, Jimenez M, Nelson R, Jackson RH Duodenal ulceration: a review of 110 cases *Arch Dis Child* 1987;62:554-8
- ² Tatsuda M, Iishi H, Okada S Effects of cimetidine on the healing and recurrence of duodenal ulcers and gastric ulcers *Gut* 1986;27:1213-8

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Enuresis in children

Sir,

I was interested to read your correspondent's personal view of her enuresis and her observations on its management.¹ One can't but help sympathise with her. In my experience most parents of enuretic children are bothered not so much by the nuisance that it causes them but by whether it could be a symptom or sign of disease in soma or psyche; if they are reassured on that score they can usually cope until the child demands to be 'cured'. As we all know, wetting can be a manifestation of many diseases: of the urinary tract, of the upper respiratory tract (obstruction at night), of the endocrine system (diabetes mellitus, diabetes insipidus, and Addison's Disease), of the gut (coeliac disease with intestinal water retention), of the cardiovascular system (improving renal perfusion at rest), of the hypothalamus (failure of development of diurnal rhythms), of the central nervous system (nocturnal or early morning fits), or of the psyche, these should be carefully excluded before the symptom is 'treated' on its own merits. For this reason, and because it represents a stigma, attendance at so called enuretic clinics may be harmful, as is the provision of a star chart—implying that the wetting is under voluntary control—or the imposition of an alarm (although this can be very helpful when managed by the child himself). Drugs like imipramine do seem to help but they bring 'magic' into the management, are dangerous in overdose, and do not have a convincing rationale in relation to bladder innervation, if indeed they do act by increasing capacity. In this context it is interesting that nearly all nocturnal enuretics are wet before their parents go to bed.

Perhaps as members of a profession whose practice is supposed to be science based we should confine ourselves

to sorting out and acting on what we do know of the pathogenesis and leave the rest to growing up, practical sympathy, education for all concerned—particularly teachers—and common sense measures to mitigate nuisance like the provision of a washing machine, using a covered mattress and easy to wash sheets (supplemented by newspapers used as blotting paper), and a potty under the bed.

Reference

- ¹ Anonymous My enuresis *Arch Dis Child* 1987;62:866-8

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Hearing loss due to mumps

Sir,

We share the opinion of Hall and Richards that mumps is a major cause of severe sensorineural hearing loss.¹ During an epidemic of mumps in Israel in 1984, 85 children with mumps were admitted to the paediatric department of the Beilinson Medical Center, which serves an area of roughly 68 000 children (age 0-14 years). Seventy nine of the patients had symptoms or signs of meningoencephalitis. Three children (3.5%) developed unilateral profound sensorineural deafness in association with mumps.

The first was a 3 year old boy who had bilateral parotitis and meningeal irritation. Cerebrospinal fluid examination showed 1020 cells/mm³ (98% mononuclear cells), and mumps virus was subsequently isolated from this fluid. During his stay in hospital his parents noticed that he did not respond to calls, and audiometry showed right severe sensorineural hearing loss.

The second patient was a 10 year old girl with bilateral parotitis, severe headache, and vomiting. On the sixth day in hospital she complained of inability to hear a telephone conversation through her right ear, and severe sensorineural hearing loss was documented by audiometry.

The third patient was a 8 year old girl who was admitted for observation with fever of 39°C. In the ward she complained of inability to hear with the right ear, and this was confirmed by audiometry. As we were aware of the association of hearing loss and mumps this possibility was tested, and her complement fixation antibody for mumps rose from 1/20 to 1/240 within three weeks, which confirmed recent infection. Routine hearing screening tests done on these three patients before the disease gave normal results. All the other children with mumps who were in hospital were tested and no significant hearing abnormalities were found.

A postal inquiry, albeit with an incomplete response, showed three additional cases of deafness after mumps in 1984, one of them with severe bilateral hearing loss

During the same year, 6534 cases of mumps were reported to the health authorities. Although one considers many unreported and subclinical infections, the occurrence of six cases of deafness due to mumps seems significantly higher than the assumed rate of 1/20 000 infections.¹ According to Sullivan *et al.*,² about 2.5% of patients with mumps may require treatment in hospital, considering this possible rate of admission the incidence of severe hearing loss associated with mumps may have been as high as 13400 cases of clinical mumps.

Two groups of patients with deafness related to infection with mumps may have been missed by the study of Hall and Richards: firstly, cases of mumps that were not apparent which are considered to be in the range of 30–40% of all infections with mumps.³ In these cases, it is impossible to obtain a history of parotitis, but, as shown by our third patient, severe hearing loss may, none the less, occur. Secondly, there are rare cases of bilateral hearing loss caused by infection with mumps.⁴ Therefore, the importance of mumps as a cause of acquired deafness may be greater than usually estimated.

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Non-convulsive status epilepticus

Sir,

We have read Manning and Rosenbloom's interesting paper concerning non-convulsive status epilepticus.¹ They report 13 patients, five of whom presented with fluctuating neurological symptoms (ataxia, dysphasia, and unresponsiveness) and developmental deterioration coinciding with continuous paroxysmal activity on the electroencephalogram. The authors stress the 'epileptic' nature of such symptoms. They have not, however, reported whether the evidence of status epilepticus was also detected on an electroencephalogram taken during sleep.

We have observed five boys and five girls with a mean age of 6 years who have long standing electrical status epilepticus during slow sleep. In six cases focal or

unilateral epileptiform activity occurred during more than 85% of non-rapid eye movement sleep, but electroencephalograms taken while they were awake disclosed only a frontal or frontal/central focus. The remaining patients presented with typical electrical status epilepticus during slow sleep characterised by a generalised epileptic pattern on electroencephalography during non-rapid eye movement sleep.² All patients had fluctuating neurological symptoms as well as disturbance of gait and motor coordination, speech impairment, behavioural changes associated with alteration in responsiveness, and developmental deterioration. All these children were suffering from epileptic seizures and were mentally retarded (six presented with congenital cerebral palsy). Remission of electrical status epilepticus during slow sleep was observed in two patients who fully recovered.

We believe that such fluctuating symptoms are not directly related to paroxysmal activity seen on electroencephalograms, but probably reflect a more complex brain disorder. In our cases a continuous epileptic activity was recorded on electroencephalograms only during sleep, while neurological symptoms were present when the children were awake. Moreover, our observations suggest that electroencephalography should be performed during spontaneous sleep in children with fluctuating neurological symptoms and mental deterioration, even if the recording made when awake did not show non-convulsive status epilepticus.

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Topical iodine, breastfeeding, and neonatal hypothyroidism

Sir,

The case of transient congenital hypothyroidism after topical iodine in pregnancy reported by Danziger *et al.*¹ confirms and extends our previous observation² that the cutaneous application of povidone-iodine (PVP-I) in mothers at the time of delivery results in iodine overload and in slight impairment of the thyroid function of their breastfed infants due to a Wolff Chaikoff effect.³ We recently observed severe transient congenital hypothyroidism in a breastfed infant born to a mother who had performed vaginal douching with PVP-I for gynaecological reasons twice a day since delivery. As shown in the figure the concentration of thyroid stimulating hormone (TSH) in serum was moderately raised at the time of systematic screening for congenital hypothyroidism, but thyroxine (T₄) was normal. Control examinations performed on days 14 and 22 showed an appreciable increase in serum TSH

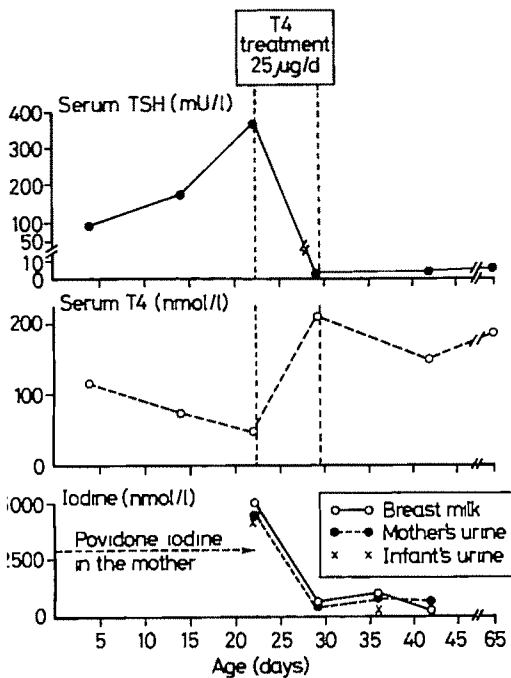


Figure Time course of the serum concentrations of thyroid stimulating hormone (TSH) and thyroxine (T4) in the infant and the iodine content of the urine of mother and infant and the mother's breast milk

and decrease in serum T4, substitutive treatment (25 µg L-T4/day) was started on day 22. Physical examination of the child was normal. The figure shows that the iodine content of maternal milk and maternal and infant urines was extremely high during the vaginal douching period but reverted to normal within seven days after withdrawal of PVP-I treatment. Breastfeeding was not discontinued. Thyroxine treatment was interrupted after seven days and thyroid function remained normal during the next two months.

We agree that iodine overload should be systematically considered as a cause of neonatal transient hypothyroidism. We recommend that urinary iodine measurement is included in the control examinations of infants with abnormal screening tests even if the possibility of iodine overload is not suspected on the basis of the history of the infant and the mother. Our case indicates that early recognition and withdrawal of iodine causing the overload results in rapid and spontaneous resolution of the Wolff Chaikoff effect. As a consequence, longterm T4 treatment, with the unnecessary stress for the family, and the risk of iatrogenic hyperthyroidism as suggested by the data of Danziger *et al* could be avoided.

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Monitoring end tidal CO₂

Sir,

Watkins and Weindling conclude that monitoring of end tidal CO₂ cannot be recommended for neonates with pulmonary disease, primarily because there are fluctuations in the alveolar arterial oxygen gradients associated with the clinical course of the disease.¹

This assumption may be correct. There are, however, other factors which may have accounted for the large PaCO₂ and PetCO₂ gradient that they found. Among these are the use of rapid ventilatory rates with low tidal volumes and high fresh gas flows, which are mentioned. Also of importance is the type of ventilator used. This is particularly so when end tidal gas is sampled proximally at the endotracheal tube connector. Infants weighing less than 8000 g and ventilated with a continuous flow, time cycled ventilator (for example, the Bourns) have large PaCO₂ and PetCO₂ gradients.² This may be partially due to the dilution of end tidal gas by the continuous flow of fresh gas past the sampling site. The capnograph waveform, therefore, either fails to reach a plateau or reaches a plateau that underestimates PaCO₂. In contrast, the use of a ventilator that automatically interrupts the flow of fresh gas at the completion of inspiration (for example, the Siemens Elema 'Servo' 900C) permits accurate prediction of PaCO₂ from PetCO₂ in infants.² The problems of end tidal sampling in children weighing less than 8000 g who are ventilated with a continuous flow ventilator can be partially overcome if sampling is performed distally, at the tip of the endotracheal tube.³

It would be of interest to know the type of ventilator used by Watkins and Weindling. It is possible that the capnometer was not measuring PetCO₂ accurately, as was assumed. End tidal CO₂ monitoring is useful during paediatric anaesthesia—it may yet be in neonatal intensive care.

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Drs Watkins and Weindling comment:

We thank Dr Stow for highlighting a potential source of error in the monitoring of end tidal CO_2 in neonatal intensive care.

He is correct in surmising that we were using time cycled pressure limited ventilators with continuous gas flow (Vickers Neovent and SLE Newborn 250). It is the practice in this unit to use a flow rate of 7 l/minute in all cases unless high pressure and ventilator rates dictate a higher rate. All except two readings were at this rate and it is of interest that these (at 10 l/minute) were both inaccurate. This infant did, however also have severe respiratory disease (alveolar/arterial oxygen difference 660 mm Hg) and so it is difficult to separate the two effects. We did find good correlations between end tidal CO_2 and $p\text{aCO}_2$ measurements in some infants with milder respiratory disease despite the continuous gas flow, and so we felt that the effect of dilution was probably minimal. Our impression is that the effect of parenchymal lung disease far outweighs other effects in these infants.

The use of time cycled, pressure limited ventilators is almost universal in neonatal intensive care units. They are cheap and simple to use, and seem to be more effective in infants with hyaline membrane disease and its complications. Experience suggests that results are better than with volume cycled devices.¹

Sampling of end tidal CO_2 from the tip of the endotracheal tube may well minimise any error due to gas flow. The majority of very low birthweight infants with hyaline membrane disease are ventilated using a 2.5 mm endotracheal tube. The luminal diameter is already critically small and considerably increases total respiratory resistance.² Any further impingement on the lumen should be avoided unless absolutely necessary.

We have already acknowledged the important role of end tidal CO_2 monitoring in anaesthetics, when most of the patients have normal lungs. This is clearly not the case in infants ventilated in a neonatal intensive care unit, in whom we feel end tidal CO_2 monitoring to be inappropriate.

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Evaluation of nebulisers

Sir,

We were interested in the paper by Tsanakas *et al.*¹ and agree that it is important to have a nebuliser with the minimum variation in output when performing bronchial challenge tests. We were concerned, however, that the authors calculated the output of the nebuliser by weighing the device before and after nebulisation. This method does not give a true idea of the output of the nebuliser. As the nebulised cloud forms there is a huge cumulative surface area formed by the aerosol droplets. Most of these droplets are returned to the nebuliser solution by a series of baffles, allowing only the finer particles to escape. At the same time some evaporation takes place. The weight loss from the nebuliser, therefore, is due to dispersion of particles of the drug, such as histamine solution, but also to evaporation. Depending on which nebuliser is used, calculating the output by weighing the device before and after nebulisation may result in an overestimate of drug output of up to 50% (unpublished observations).

To measure the output of our nebulisers we used a multi stage liquid impinger which catches the nebuliser cloud as it emerges from the nebuliser. The impinger separates the cloud into fractions comprising particles of varying sizes and we then assayed the amount of drug in each fraction, so determining not only the actual amount of drug that leaves the nebuliser but also the amount of drug in particles that are likely to reach the lungs.

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Sudden and unexpected death between 1 and 5 years

Sir,

The report by Southall *et al.*¹ that one third of the deaths in their series of infants between 1 and 5 years were unexplained begs the question of why such a common phenomenon is not more widely recognised nor apparent from the Registrar General's annual mortality figures. I think that most pathologists would concede that unexplained deaths occur throughout childhood, adolescence, and adult life although not with the frequency seen during the first postnatal year.

When the sudden infant death syndrome was officially recognised by the Office of Population Censuses and Surveys (OPCS) as a distinct entity, the rise in deaths from this cause was matched by a decline in deaths from respiratory infection.² I can only suppose that the apparent rarity of unexplained deaths between 1 and 5 years has a

similar explanation, in that what is acceptable terminology to the legal and medical professions has distressing practical consequences for parents which a pathologist must steel himself to ignore if he wishes to maintain his scientific honesty. Such honesty is, however, an essential prerequisite to any progress being made in this field. The difficulty hinges on defining an observation or measurement which can be made at necropsy and which is peculiar to the fatal condition. The nearest to this ideal in the sudden infant death syndrome is the biochemical abnormality in the composition of lung surfactant which can be shown by analysis of saline washes of the respiratory tract taken after death.^{3,4} The age distribution of 'true sudden infant death syndrome' might be more clear if this investigation were done routinely for all sudden infant and childhood deaths.

'Fever,' 'apoplexy,' and 'old age' were acceptable causes of death in an age when morbid anatomy was less sophisticated than it has since become. The terms served a valuable purpose in their time as no doubt 'sudden infant death syndrome' will be seen to have done when its pathology has been elucidated. In the meantime perhaps there is a role for a new word to cover unexplained childhood deaths (? pseudo sudden infant death syndrome). I have no doubt that were such a term to be adopted the subsequent apparent rise in the incidence of the disease would cause alarm and astonishment. What disease would necessarily decline as a consequence is something of an imponderable.

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Lower limb deformity and prevention of scoliosis in cerebral palsy

Sir,

We should like to comment on your interesting annotation.¹ Selective posterior lumbar rhizotomy reduces tone in spastic cerebral palsy. This operation, based on the technique described by Fasano *et al*² was first carried out in Cape Town in 1981 by Peacock.^{3,4} The operation is now being performed by one of us (JP) and our total experience is 131 cases.

Selection is of the utmost importance,⁴ the most striking results are observed in the spastic diplegic who walks independently with a typical diplegic gait. In these cases the walking pattern has markedly improved. The operation is also of value in more severely handicapped children. A number who could not walk are now walking independently or with walking aids, others have improved posture and mobility, and even those who have no independent mobility or voluntary function can benefit by reduction of tone in the legs. Care must be taken with those children who use spasm for supported standing and walking and have poor underlying power.

Good physiotherapy is necessary before and for a prolonged period after rhizotomy. Although the benefits can be seen immediately, it is apparent from a long term follow up study currently in progress, that the re-education of abnormal motor patterns is of the utmost importance, as is the building up of strength in weak muscles. Improvement has continued up to six years after the procedure.

Some of the children in our series had had orthopaedic surgery before rhizotomy, others had apparent fixed joint contractures. Many patients were less contracted or their 'contractures' had disappeared after rhizotomy, but appliances or orthopaedic surgery, or both, are still necessary in some cases. The reduced tone plus weak ankle musculature may produce valgus foot deformities and appliances (usually ankle foot orthoses) may be necessary.

We know of no child who has had subluxation or dislocation of hip after reduction in tone, and there has been no deterioration in those cases that had such problems before rhizotomy. No case of scoliosis or other back problem has developed. One quadriplegic without voluntary function or mobility who received only early intermittent physiotherapy and subsequently was left lying in one position has become windswept.

Though rhizotomy only deals with one aspect of a complex disorder, we are impressed by its usefulness in relieving spasticity. Physiotherapists, parents, and those children old enough to remember what their limbs felt like before rhizotomy, are enthusiastic about the results of the operation.

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Book reviews

Clinical Pediatric Otolaryngology. T J Balkany and N R T Pashley Pp 509 £46.50 hardback. C V Mosby Co, 1986.

This multiauthor contribution includes many authors from Colorado, but also others from a variety of North American centres. The book seems well-constructed and edited. There is a feeling of uniformity between the chapters by different authors that is often lacking in multiauthor textbooks. Moreover, the editors themselves have made significant contributions that are dispersed throughout the book.

It covers most aspects of paediatric otolaryngological practice, which is increasingly developing as a separate subspecialty within our field. After many of the chapters there are flow charts that will help residents in training. References are sometimes brief, and some of the illustrations are rather inadequate and some sections lack illustrations where they may have been helpful. The introductory section on general consideration is perhaps the weakest, and the chapter on allergic disease is particularly superficial in context considering the importance of the subject. There is, however, a useful contribution on the otolaryngological manifestations of systemic disease. The chapters on ear disease reflect a sensible approach to management but brevity in some sections is the limiting factor. The difficult question of mastoidectomy certainly merits inclusion of a wider variety of surgical options.

There is a full and interesting contribution on dentofacial development and upper airway obstruction that I particularly enjoyed. It is always unfortunate to see illustrations reproduced from other textbooks, especially if they are less than perfect as is the case in the section on nasal and sinus disease. By contrast, inclusion of other relevant diagrams in the section on laryngology may have enhanced the text. A further criticism of brevity might be levelled at the chapter on tumours and cysts of the neck. Generally the text is complete and easy to read but at a fairly basic level of scientific content. Nevertheless, at this price it is a reasonable purchase that will satisfy the needs of students and trainees in otolaryngology and paediatrics. It will shortly have to compete with a UK edition of Scott Brown, however, which now has a

volume devoted to paediatric otolaryngology. Most departments should purchase both volumes to be in a position to evaluate management regimens on each side of the Atlantic.

A R MAW

Orthopaedic Management in Cerebral Palsy. Eugene E Bleck Pp 497. £28.00 hardback. Blackwell Scientific Publications, 1987.

This volume is concerned with a description of orthopaedic management in its widest sense of children and young people with cerebral palsy rather than with details of orthopaedic surgical procedures. Its aim is to present a relevant perspective on cerebral palsy to orthopaedic surgeons and also to physicians and therapists. As a result the first portion of the book is concerned with descriptions of cerebral palsy and its functional effects, how function can be assessed both clinically and by special investigations, and underlying neurobiological processes so far as these are understood. From this platform a detailed account is constructed of the outlook that can be expected for individuals affected by cerebral palsy and hence of the treatment and management goals that can reasonably be attempted. This section deals critically but fairly with the many physiotherapy systems that are available and advocated, and there is also a relatively brief discussion on the usefulness, or otherwise, of the wide array of aids and appliances including orthoses that are or have been in common usage. There follows three detailed sections on spastic hemiplegia, spastic diplegia, and where there is total body involvement. In all of these the details of various orthopaedic procedures are described and placed within the context of the overall management of individual patients. Professor Bleck's personal views and experiences give an authoritative and welcome air to this section of the book.

This is an important and useful volume. Its strengths are its perspective on the place of orthopaedic surgery in the management of cerebral palsy, its personal and critical evaluations of specific surgical procedures, its recognition of what 'science' can and

cannot offer in this field, and its emphasis on the need for appropriate team work to include both the patient and his family as well as professionals. The linguistic style makes for easy reading and the cited references are full. The book can be recommended for physicians, surgeons, and therapists who have an interest in cerebral palsy as it is primarily a very helpful overview of orthopaedic management and is also a reference in respect of the place of individual surgical procedures.

L ROSENBLUM

Medical and Experimental Mammalian Genetics: A Perspective. Edited by V A McKusick, T H Roderick, J Mori, N W Paul Pp 358: \$69.50 hardback. Birth Defects: Original Article Series. Volume 23, Number 3 Alan R Liss Inc, 1987.

This is a collection of 14 papers to mark the first 27 years of a course held at the Jackson Laboratory on the beautiful coast of Maine. This 'Bar Harbor' course brings together medical and experimental mammalian geneticists and underlines the fact that they share much in terms of methods and research goals. This book shows the common areas and gives a glimpse of the enormous rate of progress in our understanding in these fields in recent years.

The first chapter gives a historical perspective on mammalian genetics referring mainly to progress in gene mapping. Papers on mammalian chromosomes, techniques of gene mapping, and the study of mutations follow. Evolution, both molecular and by the study of fossil records, is discussed in two fascinating chapters, and the help given to those investigating human disease by the study of mouse models is well described.

Of particular interest to those involved in the care of patients are the excellent papers by Cavenee on recessive mutations at human cancer loci, particularly retinoblastoma and Wilms' tumour, but likely to be applicable soon to other cancers, and by Wallace on diseases likely to be due to mitochondrial genes. Showing that it is not all theory there is a review of the detection of genetic disorders by DNA analysis,

which is now somewhat out of date because of the enormous rate of progress, and there is also speculation on the possibility of gene therapy. The editing, presentation, and illustrations are excellent. I enjoyed reading this overview of where mammalian genetics 'was at' in 1986

DIAN DONNAI

Diagnosis and Management of Seizures in Children. Gregory L Holmes Pp 293. £26.95 hardback. Bailliere Tindall, 1987

This single author book is volume 30 in the *Major Problems in Pediatrics* series and is well up to the standard of previous volumes in content and production. It is aimed primarily at the (North American) paediatrician and family practitioner but is equally appropriate for the British hospital or community paediatrician, whether established or in training. The author gives a comprehensive detailed account of the childhood epilepsies that could hardly be bettered. He is up to the minute in description, classification, and management. I found little to disagree with and many of my hobby horses are ridden with equal force and gusto. His accounts of the techniques and significance of electroencephalography and the pharmacology of anti-epileptic drugs are models of clarity with brevity. But he is equally at home with the clinical aspects and his straightforward descriptions, chapter by chapter, of non-epileptic episodic phenomena and of each of the childhood epilepsies are evidence of considerable clinical experience as well as a wide knowledge of the literature. His style is terse and easy to follow. There are many well constructed tables and diagrams that further clarify his meaning. The illustrations from electroencephalography are well chosen and well reproduced, which is often not the case in other publisher's texts. As a reference source it is excellent: the references are plentiful, well chosen and non-parochial, arranged in alphabetical order at the end of each chapter, and include some from 1985.

The European reader will inevitably compare this book with Niall O'Donohoe's *Epilepsies in Childhood* (2nd edition 1985),

which has established itself as the paediatrician's bible in the subject on this side of the Atlantic. This book is more prosaic and one misses O'Donohoe's occasional poetic asides, apt historical quotations, and penetrating insight into the psychosocial aspects of the subject. Holmes is uniformly down to earth, and he scores in his excellent handling of the basic scientific aspects. But both books are comprehensive, clear, readable, and up to date, and at a very similar price each is excellent value and ideally each paediatric department should have both volumes on their shelves.

BRIAN BOWER

Childhood Asthma. Pathophysiology and Treatment. Edited by David G Tinkelman, Constantine J Falliers, Charles K Naspitz Pp 385: \$89.75 (USA/Canada), \$107.50 (all other countries) hardback Marcel Dekker, 1987.

Childhood asthma is a disturbance of physiology brought about by a complex interaction of environmental influences on a genetic background. An understanding of reactive airways disease at this age requires a bringing together of knowledge from many disciplines including pathophysiology, biochemistry, and epidemiology as well as clinical diagnosis and treatment. This multi-author book succeeds well in providing this broad based account of childhood asthma. There is a good balance between the basic sciences and clinical information, and there are lists of references to much recent work of importance.

The contributions on defence mechanisms of the lung and the role of inflammatory mediators in the regulation of airway calibre are particularly interesting. The British paediatrician may find less new information in the clinical chapters: for instance, the phrase 'not all that wheezes is asthma, however, almost all that wheezes is asthma' has a certain familiarity. The drug treatment of asthma has a North American flavour with as much discussion on theophyllines as β adrenergic agents and as much space devoted to ketotifen as sodium cromoglycate. There is much discussion on non-pharmacological approaches to the management of asthma (includ-

ing allergen control) but rather less on patient education and compliance. Although the index is poor (neither 'cough' nor 'eczema' is listed), this book is a very valuable contribution for all paediatricians dealing with childhood asthma.

J J COGSWELL

Atlas of Pediatric Physical Diagnosis. Edited by Basil J Zitelli and Holly W Davis. Pp 486: £65.00 hardback. Edward Arnold, 1987.

The title of this huge North American volume is misleading as it is a well illustrated textbook and not just a collection of illustrations. The text is extensive and extends well beyond the frontiers of diagnosis. Despite the high proportion of text, the large typeface and masses of mainly colour illustrations combine to give the book enormous visual appeal. The book is a pleasure to handle and easy to read. It is divided into 20 chapters covering most aspects of paediatrics, but there are no sections on oncology or malformation syndromes. The best sections are those on oral disorders, orthopaedics, and ear, nose, and throat. Those on gastroenterology, genetics and chromosomal disorders, and developmental paediatrics are especially weak. Not all sections lend themselves to photographs of patients. The chapter on cardiology contains numerous radiographs (especially barium swallows), and haematology is mainly illustrated by blood films.

Sadly too many illustrations are spoiled or obliterated by a pink or red hue, and several fail to show what is intended—for example, there is a nice colour illustration of a hypopigmented area of skin in a patient with tuberous sclerosis, the lesion becoming invisible on the matching picture taken under a Wood's light. Six pages describe the diagnosis and assessment of asthma in considerable detail but omit to mention measurement of the peak expiratory flow rate. Nurses and medical students will enjoy this book most; postgraduates are likely to find the sub-specialty sections the more useful and interesting.

T J DAVID

British paediatrics

The British Paediatric Association: 60 years

The British Paediatric Association (BPA) celebrates its Diamond Jubilee this year. The Association was founded by a group of six eminent paediatricians at a meeting in George Frederic Still's house in Queen Anne Street, London on 2 February 1928. Still was the accepted leader of the small band of physicians who were interested in the diseases of children and was the natural choice for president of their Association. Donald Paterson, who conceived the idea of a paediatric association and was the driving force in the enterprise, was unanimously elected honorary secretary. The founder members included such well known personalities as Hector Cameron, Robert Hutchison, Leonard Parsons, Bernard Schlesinger, and James Spence.

The BPA has planned a series of events during the year to commemorate this important milestone in the history of British paediatrics. The first of these will be a reception for past and present officers of the Association in February. In March a press

conference will be held to launch the Diamond Jubilee book, *Child health in a changing society* edited by the current president, John Forfar. At the Jubilee scientific meeting at the University of York in April the publication of the latest volume of the History of the BPA will be announced, and in May a reception will be held at the House of Lords.

During October there will be a Child Health Week to celebrate the achievements of the child health services and to publicise the work of paediatricians, a service will be held in Westminster Abbey, and the celebrations will conclude with a conference and dinner at the Royal College of Physicians of London.

Further details of all these events will be announced by the BPA during the year and this page of the Archives will feature a series of related reports and reviews.

ADM JACKSON

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

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Annotations

Immunisation for the immunosuppressed child

In this day and age any death from measles is bad enough but when it happens to a child in remission and potentially cured of a lethal disease like leukaemia it is a particularly tragic and unnecessary loss. Most children should have been immunised by the time leukaemia develops so that each of these preventable deaths, and there are quite a number of them each year, can be viewed as a shameful indictment of our failure to implement an effective programme of immunisation. Our poor record has been the subject of considerable analysis and comment and, sadly, it seems that doctors and nurses must take a major part of the blame.¹⁻⁴ All too often immunisation is refused because of apathy about the disease, from ignorance about the vaccine, from misinterpretation of the few genuine contraindications or, from the invention or propagation of contraindication 'myths'. Unfortunately, a sense of responsibility to ensure that a child is protected against a potentially serious disease may too easily be subordinated to exaggerated fears about the possible medicolegal consequences of a vaccine reaction.

Recent reports about measles in immunosuppressed children document this serious problem and are timely reminders of the uncertainty that exists about the appropriate programme of immunisation for these children.^{5,6} Doctors attempting to give clear guidance to parents are faced with conflicting advice from experts and a noticeable lack of relevant data. Nevertheless, based on common sense and accumulated experience especially from the United States, a few positive statements are possible:

- Measles vaccine and other *live* virus vaccines such as mumps, rubella, and oral poliomyelitis vaccine must not be administered to patients who are immunodeficient or immunosuppressed. Included in this prohibition are children suffering from congenital immunodeficiency disease and children suffering from malignant conditions such as leukaemia, lymphoma, Hodgkin's disease, or other tumours of the reticuloendothelial system and children receiving chemotherapy, high dose corticosteroids, or other immunosuppressive treatment, including radiation.

- Killed inactivated vaccines (diphtheria, tetanus, pertussis, and inactivated polio vaccine) are safe for immunosuppressed children and the

immune response, though less than in normal children, will confer some protection. The usual primary course of three injections of triple vaccine (adsorbed diphtheria vaccine, tetanus and pertussis) should be given along with inactivated polio vaccine at the appropriate times if no other contraindications exist. It is particularly important that immunosuppressed children are given inactivated polio vaccine for foreign travel, and for some countries typhoid and hepatitis B vaccines (both inactivated) should also be considered. Children with congenital deficiencies of immune function may be incapable of responding to vaccines and should receive regular doses of immunoglobulin, usually once a month.

- Experts disagree on the length of time that should elapse between withdrawal of immunosuppressive treatment and the administration of live vaccines. Periods between three months and two years have been quoted. It is probably safe to use live vaccines six months after treatment has stopped as this allows a reasonable margin for the return of immune responsiveness. Nevertheless some prefer to wait for at least a year and in individual cases the child's haematologist or oncologist should be consulted before any decision on immunisation.

- Children with diseases not associated with an impaired immune system may become immunocompromised from steroid therapy. These children should be considered individually according to the dose, route of administration, and duration of treatment. If treatment is with inhaled steroids or with low to moderate doses of short acting systemic steroids either daily for short periods (under two weeks) or on alternate days for longer periods, they can receive live virus vaccines as can children being treated with topical steroids. Children receiving large amounts of systemic steroids (2 mg/kg) for periods longer than one week should not be given live virus vaccines until at least three months after treatment has stopped.

- The effect on immunity of a superimposed malignant condition and its treatment is poorly understood. Children who have had measles or have been immunised seem to remain relatively immune during treatment for leukaemia but the duration of this immunity is uncertain. We need more data on the persistence of immunity to determine if these children should be reimmunised at a later date.

● Immunodeficient or immunosuppressed children in contact with infectious disease should be given the appropriate prophylactic immunoglobulin as soon as possible. Human normal immunoglobulin and specific immunoglobulins—for example, varicella zoster immunoglobulin—are available. A preparation of concentrated human measles immunoglobulin is available in Scotland. Children who develop chickenpox should be treated with acyclovir.

● At the time of first diagnosis of leukaemia or other forms of childhood cancer, a good immunisation history is essential. Serological evidence of immunity, or lack of it, to measles, mumps, rubella, and chickenpox should be documented. If there is any doubt either from the history or serology, the child should be considered as non-immune and protected accordingly.

● Parents should be encouraged to make sure that the child's siblings are appropriately immunised. Although recipients of measles vaccine are not normally infectious to others, some experts consider it prudent to restrict contact with the immunosuppressed child patient for two weeks after immunisation. Siblings who have not been immunised against polio must be given inactivated polio vaccine instead of the oral vaccine.

● Children with cancer are encouraged to lead as normal a life as possible. This includes return to school as soon as treatment allows where they will be at risk from unimmunised playmates and classmates. Doctors should seek and encourage the cooperation of other parents in achieving a high level of measles vaccine uptake within the school and neighbourhood.

● Varicella vaccine is not yet available for general use but has been used to protect vulnerable children during maintenance treatment for solid tumours. Its exact role in childhood leukaemia remains uncertain and at the present time varicella zoster immunoglobulin probably offers the best protection to varicella contacts with acyclovir being used in treatment of the developed infection.

Human immunodeficiency virus (HIV) infection and immunisation

Recent concerns about HIV infection and acquired immune deficiency syndrome (AIDS) have included attention to the problems of immunisation. Official advice inevitably lags somewhat behind practical experience in such a rapidly changing clinical scene. Recent evidence indicates that, at the time of writing (November 1987):

(1) Symptomatic HIV antibody positive children (in contrast to children known to be immunosuppressed for other reasons) may (a) be given live virus vaccines, *except* BCG, as the benefits of protection from the natural infections appear to outweigh the risk from the vaccines, especially in communities where the infections are still prevalent,⁷ and (b) should receive all appropriate inactivated vaccines. Thus infants should be protected by immunisation with oral poliomyelitis vaccine and measles vaccine at the appropriate times and should receive diphtheria, tetanus, and pertussis vaccines in accordance with current recommendations. There is no evidence that immunisation accelerates the course of HIV infection.

(2) Asymptomatic HIV antibody positive children (a) should be given live vaccines according to current indications with the exception of BCG, and (b) should receive inactivated vaccines when indicated.

(3) Children whose parents or other household members are known to be immunocompromised for whatever reason should be given inactivated poliomyelitis vaccine.

(4) Unimmunised children with AIDS or other clinical manifestations of HIV infection are at serious risk from infectious diseases such as measles and varicella. If exposed to these infections they should be given passive immunisation with the appropriate immunoglobulins.

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Tests for detecting and monitoring the acute phase response

Children with inflammation due to infection or other tissue damage develop a systemic response which includes fever, a neutrophil leucocytosis, and an increase in concentration of several plasma proteins of hepatic origin. These changes are collectively known as the acute phase response and are mediated by cytokines, such as interleukin-1 and tumour necrosis factor, which are synthesised by macrophages that accumulate at the site of tissue damage.¹ The term acute phase is ill defined but refers to the intensity rather than the duration of the inflammatory response so that a child with chronic disease may also show an increase in acute phase reactants, either intermittently or persistently.

The specificity of the acute phase response means that measurement of an increase in plasma concentration of acute phase proteins provides unequivocal evidence of inflammation and, because of the ubiquitous nature of inflammation, may therefore be used to detect a wide range of organic diseases. While bacterial infection is one of the most potent stimuli of the acute phase response, immunological, traumatic, ischaemic, or malignant damage to tissues usually evokes inflammation and thus a response. The magnitude of that response provides a guide to the intensity of inflammation or the extent of tissue involvement.² Measurement of acute phase proteins may thus be used for either detecting organic disease, assessing the extent or activity of that disease, monitoring treatment, predicting outcome, or detecting intercurrent infection.

Laboratory tests

In paediatrics the main value of tests for detecting and monitoring the acute phase response is as an early indicator of bacterial infection in circumstances where a microbiological diagnosis is impossible or delayed. Other applications for such tests are similar to those in adults and include the monitoring of chronic inflammatory disorders such as Still's disease. It is essential to appreciate that, while the acute phase protein response is highly specific for inflammation, many disease processes are accompanied by inflammation so that a rise in acute phase proteins can *never* be specific for a particular disease, such as infection, and *must* always be interpreted in the light of the clinical picture.

The variety of tests available to monitor the acute

phase response has led to controversy over which tests should be used. The poor specificity of fever is well known and determination of total and differential leucocyte counts is of limited value in the diagnosis of bacterial infection in children,^{3–6} although the immature:total neutrophil ratio may be more useful.⁷ The major area of debate, however, concerns tests for detecting an increase in acute phase proteins, the leading contenders being measurement of an individual acute phase protein, such as C-reactive protein, or tests such as the erythrocyte sedimentation rate and plasma viscosity that provide an integrated measurement of the contribution of several proteins.

Individual acute phase proteins vary not only in the rate at which their blood concentration rises after the onset of inflammation, but also in half life and in rate of catabolism in different forms of inflammation. C-reactive protein, serum amyloid A protein, and alpha-1-antichymotrypsin rise within 6 to 10 hours of injury, show large incremental increases of 10 to 1000 fold over their normal values, have short half-lives, and behave consistently in different forms of inflammation. Orosomucoid, alpha-1-antitrypsin, haptoglobin, and fibrinogen rise after 24 to 48 hours, rarely increase more than two fold, have long half lives and, with the exception of orosomucoid, show variable catabolism in some diseases. Haptoglobin and alpha-1-antitrypsin have common genetic variants which result in their deficiency. C3, C4, and caeruloplasmin generally show poor and inconsistent acute phase responses.

Of the useful acute phase proteins C-reactive protein is the most easily measured, and commercial assay kits are widely available. Unfortunately, studies of its usefulness have been bedevilled by poor standardisation and the use of non-quantitative assays. Now that an international reference standard for it has been accepted by the Expert Panel on Biological Standards of the World Health Organization there should be better standardisation of the assay between laboratories and in future clinical studies. Much of the value of measuring C-reactive protein lies in serial monitoring of the onset or resolution of inflammation and this necessitates quantitative assays rather than semi-quantitative or qualitative latex agglutination tests. Techniques that give the required rapid results include laser nephelometry (1.5 hour assay time), rate immunonephe-

lometry or turbidimetry (0.25–0.5 hour), and enzyme immunoassay (0.25 hour).

The erythrocyte sedimentation rate is probably still the most widely measured index of the acute phase response. The relative contribution of different plasma proteins to erythrocyte sedimentation are fibrinogen 55%, alpha-2-macroglobulin 27%, the immunoglobulins 11%, and albumin 7%. The test is also affected by red cell characteristics and, in particular, their number, with a decrease in haematocrit increasing the erythrocyte sedimentation rate. Plasma viscosity, though not yet widely used, is unaffected by red cells and, unlike the erythrocyte sedimentation rate, may be measured on stored samples. It reflects primarily the plasma concentration of fibrinogen and immunoglobulins. Both tests are thus non-specific and reflect changes in a number of proteins, of which the acute phase reactant component is predominantly fibrinogen. Thus, in parallel with changes in fibrinogen concentration, both tests respond slowly to inflammation, not showing an increase until 24 hours or more after the onset and falling slowly to normal with a half time of 96–144 hours on resolution of inflammation. They do, however, also respond to increases in immunoglobulins, immune complexes, and other proteins and thus cast a broader net for the detection of disease than does any acute phase protein alone. They have the advantage of being less affected by acute events, such as a viral infection, that cause a transient increase in sensitive acute phase proteins such as C-reactive protein.

Tests of erythrocyte sedimentation are, however, not well suited to paediatric use owing to their requirement for a relatively large blood sample, although microsedimentation tubes that require a smaller volume of blood are available and published evaluations^{8–10} have shown acceptable correlation with the selected Westergren method of the International Committee for Standardization in Haematology.¹¹ In addition, the sensitivity of the erythrocyte sedimentation rate to haematocrit means that neonatal polycythaemia and childhood anaemia will give false low and false high values respectively. Hypofibrinogenaemia of the newborn may also cause false low results for both erythrocyte sedimentation rate and plasma viscosity.¹² Of the two tests plasma viscosity is more suited to paediatric practice but instrument manufacturers have been slow to develop automated viscometers for clinical use and the sedimentation rate is still widely used because it is available.

Acute disease and infection

When the clinical history is of less than 24 hours'

duration, C-reactive protein is the acute phase protein of choice owing to its rapid response (6–10 hours) and large incremental increase from concentrations of less than 10 mg/l in normal serum (including that of premature infants and neonates). Typical serum concentrations would be: mild inflammation and severe viral infection, 10–40 mg/l; active inflammation and bacterial infection, 40–200 mg/l; and severe bacterial infection and burns, 200–400 mg/l.

Measurement of C-reactive protein is of particular value in paediatric practice as an indicator of invasive bacterial infection (viral infection causing little or no increase) and the subsequent fall in serum concentration (half time of 48 hours) on resolution of the inflammatory focus is useful for monitoring the efficacy of treatment. There is no absolute serum concentration of C-reactive protein that is diagnostic of bacterial infection, although 40 mg/l has been claimed to give higher specificity, with acceptable sensitivity, than 20 mg/l. In a study of 31 children who had been febrile for more than 12 hours, a serum concentration of 40 mg/l or more on admission had a sensitivity of 79% and a specificity of 90% for the detection of bacterial infection, while an erythrocyte sedimentation rate of 30 mm/hour or more had a sensitivity of 91% and a specificity of 89%.¹³ A similar study of infected neonates clearly showed that sensitivity varied with the level of C-reactive protein considered, the definition of infection used, and the time at which the blood was taken in the course of the disease.⁷ Specificity also depends on whether patients with obvious non-infective pathology are excluded from the study group, as they clearly should be,¹⁴ and on whether serial measurements are made.¹⁵ In a study of children with suspected meningitis a serum concentration of 20 mg/l or more indicated a bacterial rather than viral origin.¹⁶ In immunocompromised patients with leukaemia concentrations of 30 mg/l¹⁷ and 100 mg/l^{18–20} have been used to diagnose infection. In premature rupture of the membranes a C-reactive protein concentration of greater than 125 mg/l gave a positive predictive value of 96% and a negative predictive value of 89% for chorioamnionitis and, owing to the poor success rate of amniocentesis, was felt to be the more useful diagnostic test in this clinical situation. Interestingly the erythrocyte sedimentation rate showed a positive predictive value of 100% and a negative predictive value of 67% in this study.²¹

Measurement of C-reactive protein is most useful in the rapid diagnosis of infection if serial quantitative measurements are made and a progressive increase can be shown in the first 48 hours. If single measurements are used their value lies in excluding

or confirming infection 24 hours after the first clinical symptoms, at which time the erythrocyte sedimentation rate may give similar information

Chronic disease

In the diagnosis of chronic disease there may be an intermittent or persistent increase in acute phase proteins but the nature of the hyperproteinaemia is more complex than in the first 24 hours of an illness and no single acute phase protein can be considered to be representative. Such tests as those that measure erythrocyte sedimentation rate and plasma viscosity, being sensitive to the combined effect of several acute phase proteins and immunoglobulins, should therefore be used. Although changes in response to treatment are more rapidly mirrored by C-reactive protein, erythrocyte sedimentation rate and plasma viscosity have the advantage of being less affected by intercurrent illness such as a minor infection. A combination of C-reactive protein and either erythrocyte sedimentation rate or plasma viscosity may therefore provide the most useful information on which to base therapeutic intervention.²

Conclusion

No one laboratory test satisfactorily reflects all aspects of the acute phase response and the choice of test is determined by the length of clinical history and the nature of the disease process. Serial measurement of C-reactive protein by a rapid, quantitative, and appropriately standardised assay is the test of choice for detecting and monitoring the acute phase protein response of acute inflammatory disorders such as infection in children. The assay is only worthwhile as a screening procedure for infection if the clinical context is well defined and other clinically detectable inflammatory diseases are excluded. With these provisos, a concentration of C-reactive protein above 40 mg/l may be used to confirm infection, its diagnostic value increasing with time after the onset of symptoms to a maximum at 48 to 72 hours. In contrast, diagnosis and monitoring of chronic inflammatory disease is best undertaken by the measurement of erythrocyte sedimentation rate or plasma viscosity, although measurement of C-reactive protein may be useful in detecting an early response to treatment.

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The highly talented child

Indulgence or necessity

It is perhaps an indulgence of the western world that there should be an interest in the problems of the talented child, but an interest there is, and a justified one at that. Whether the special aptitude be in studies, sport, music, arts, or any combination of these, the potential for problems is high. For example, teacher recognition of gifted children (that is, an intelligence quotient above 140) is less than 50%.¹ In consequence, some children lose interest, fall behind, and may even be deemed unintelligent. Others may be pushed to achieve by parents or teachers to the point that their emotional development may be impaired in the pursuit of academic excellence; a 12 year old studying for an honours degree at Oxford University is clearly misplaced. Alternatively, their obvious exceptional intelligence sets them apart from their peers who in turn see and treat them as odd and different.

The pressure to achieve is often more noticeable in children whose special aptitude is in sports or arts. Intensive training can interfere with regular schooling and studies, and may prevent a child from either making or keeping friends.² Parents may, understandably, get vicarious satisfaction from their child's achievements and in so doing impose undue pressures. Such pressure may be overt or more subtle, in the form of 'we only ask that she do her best'. This innocent statement may be responded to by the child as 'I always have to do my best', 'How do I know what is my best?' 'What happens if I don't do my best?' Many children cope quite satisfactorily under such pressure; but for others, perhaps rendered vulnerable by a combination of personality, temperament, and external pressures, the stress of achievement, performance anxiety, and the attendant expectations and demands on time and energy gradually erode the child's sense of well being. If we adults never allowed ourselves an off day for fear of letting down others we too would experience high, or perhaps intolerable levels of stress and distress. So it is with highly talented children. Some may have the courage or bloody mindedness to refuse the continuing pressures. Others, more conforming or compliant cannot rebel and so develop other means of escape.

Stress reactions

Where an organic substrate is present a physical

response to stress readily occurs. Physiologically vulnerable children may develop a wide range of physical symptoms in response to a fear of failure or loss of parental approval.³ Recurrent injury may serve as a socially acceptable form of withdrawal from stressful situations.⁴ Anorexia nervosa or related eating disorders are more common in female gymnasts and ballet dancers because of the preoccupation with diet, fitness, and body shape.⁵

Such reactions are often heavily disguised. In a two year period Wolff and Lask saw 21 children between the ages of 9 and 15 with physical symptoms that had defied explanation despite intensive organic and psychological investigation.⁶ The factor that each child had in common was that they had failed to recover from a relatively minor injury, illness, or viral infection, and remained symptomatic for up to four years. They were all high achievers and only lengthy and patient discussions with the child brought out the intense stresses hidden by the sense that they must not fail, complain, or be anything but perfect. Such behaviour tends to be subtly reinforced by the parents who promote the same values.

Where no obvious organic substrate exists other stress reactions may be apparent. A 12 year old competitive swimmer whose father insisted on seven days a week intensive training started hearing voices telling her not to swim. A 14 year old junior cross country champion developed an obsessional-compulsive disorder, which included having to take two steps back for every one forward.

Management

The onus on the paediatrician is in recognising such problems. A comprehensive approach to assessment⁷ will eventually unravel the mysteries of any unexplained illness⁸ and the hidden problems of the highly talented child.⁶ Children who excel have special needs whatever their area of excellence.² We need to advise parents, teachers, and coaches that highly talented children have emotional, educational, and interpersonal needs that may surpass those of their less talented peers. Intellectually gifted children may benefit from special educational provision.¹ Parents should define in a measurable way what they expect—will they be disappointed if their child gets 70% rather than 90% in an end of year exam? Will it matter if she comes fourth rather than first in a piano competition? Does failure to be

picked for a representative team matter? If the answer is no, how can they convince their child they mean it? If the answer is yes, how can they modify their own expectations?

When levels of anxiety are high time should be found on a regular basis when the parents can discuss the causes of concern and attempt to find solutions. Self-relaxation is valuable when stress is producing physical symptoms such as headache, abdominal pain, or diarrhoea. Where stress is too high (for example, when illness supervenes, or education suffers) clear advice is required that pressures must be reduced, and the child's talents not exploited. Above all, days off and off days must be acceptable and even encouraged!

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Original articles

End stage renal failure: 14 years' experience of dialysis and renal transplantation

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SUMMARY One hundred and thirteen children (59 boys and 54 girls aged from 2 to 16 years) with end stage renal failure entered the renal dialysis and transplantation programme between 1972 and 1983. They were followed up until December 1985. Ninety eight children were initially treated by haemodialysis in hospital and 15 by renal transplantation. The average wait on dialysis was seven months (range 0-43 months). One hundred and six children were given 129 renal transplants, 32 of which were from living related donors.

At the end of 1985 54 of the 113 patients (83%) were alive, 81 (72%) with functioning grafts, 11 (10%) were receiving haemodialysis in hospital, two (1%) were being treated by continuous ambulatory peritoneal dialysis, and three had been lost to follow up. The 14 years actuarial survival was 81%. Four patients receiving dialysis and 12 who had received transplants died, a mortality of 14%. The main complications of treatment were retardation of growth in 49 (43%), hypertension in 75 (66%), and osteopathy in 36 (32%). Retardation of growth could not be reversed by successful renal transplantation. Seventy two patients (88%) assessed their health as good to excellent, and 9 (7%) as poor. Patients with a functioning graft did much better than those receiving dialysis. Treatment of end stage renal failure led to full rehabilitation in most patients and renal transplantation was more effective than dialysis.

A study by the Arbeitsgemeinschaft fuer Paediatrische Nephrologie showed that in West Germany each year about five children per million develop end stage renal failure.¹ Similar data were collected from the paediatric registry of the European Dialysis and Transplantation Association.²

During the past decade dialysis and renal transplantation have both become accepted forms of treatment of end stage renal failure. Long term results have usually been reported separately for paediatric haemodialysis³ and renal transplantation.⁴⁻⁷ There have been only a few surveys of the overall outcome of all children treated for end stage renal failure.⁸⁻¹⁰ This report describes the 14 years' experience (1972-1985) of a single paediatric centre for dialysis and renal transplantation. The children's hospital of the medical school in Hannover was built in 1972 and soon became a referral centre for patients with end stage renal failure, serving a large area of northern Germany.

Patients and methods

One hundred and thirteen children with end stage renal failure were accepted for treatment during the period 1972 to 1983 and were followed up until the end of 1985. The number of new patients treated annually is shown in table 1. Eighteen children who received transplants had first received dialysis at other centres. Eight other children with end stage renal failure were seen during the period, but not accepted for treatment. In four dialysis was not considered because of the age and size of the infant; this was before the development of techniques for long term peritoneal dialysis. Three children were excluded because of severe mental retardation and one because of severe heart disease. The decisions to exclude these patients were made with the full agreement and informed consent of the parents.

The children were between 2 and 16 years old when they started treatment. The initial treatment

Table 1 Number of new patients with end stage renal failure treated annually, 1972-83

Year	No of patients receiving dialysis	No of patients receiving one transplant	No of patients receiving two or more transplants
1972	1	1	0
1973	5	2	0
1974	2	3	1
1975	6	2	0
1976	6	12	0
1977	13	9	3
1978	8	11	2
1979	13	12	1
1980	11	16	1
1981	6	9	5
1982	8	12	4
1983	19	14	0

was haemodialysis in hospital ($n=98$) or renal transplantation ($n=15$). The youngest child accepted for long term haemodialysis was 2.9 years old and the youngest to have a renal transplant was 2.2 years old. The mean (SD) age at the start of treatment was 10.9 (3.3) years. The sex and age distributions of the 113 children are shown in table 2. The diseases causing the end stage renal failure are summarised in table 3. Ten children (9%) presented with acute renal failure¹¹ and 103 (91%) with chronic renal failure. In a few children the original diseases were associated with moderate mental retardation, deafness or blindness; these were not considered as contraindications to treatment. The risk of recurrence of the original disease in the transplanted kidney was not a contraindication to transplantation.

Sixty five children were already being seen in a paediatric clinic before they developed end stage renal failure; 26 of these were being seen in this centre, and they had a mean creatinine clearance of 26.4 ml/minute/1.73 m² body surface. Forty eight children entered our treatment programme after developing end stage renal failure, and 18 had already received dialysis in other units. When the creatinine clearance in children weighing more than 20 kg approached 10 ml/minute/1.73 m², a vascular access route was created. At the same time tissue typing was performed and three units of packed red cells were transfused. When the creatinine clearance fell to 5 ml/minute/1.73 m² the children were entered in the Eurotransplant Registry. If the parent donated the kidney no arteriovenous fistula was created.

DIALYSIS

The vascular access used for haemodialysis was a subcutaneous Cimino fistula at the forearm in 51

Table 2 Age and sex of 113 patients with end stage renal failure

Age (years)	No of boys	No of girls
2	2	0
3	1	1
4	0	1
5	1	2
6	3	2
7	4	3
8	8	8
9	3	6
10	6	6
11	5	6
12	4	7
13	7	4
14	4	3
15	7	5
16	1	3

Table 3 Diseases leading to end stage renal failure in 113 children

Disease	No of patients (%)
Congenital or familial	
Hypoplasia or dysplasia	18 (16)
Cystinosis	16 (14)
Nephronophthisis	15 (13)
Obstructive uropathy	10 (9)
Familial nephritis	7 (6)
Oxalosis	3 (3)
Infantile cystic kidneys	2 (2)
Acquired	
Proliferative glomerulonephritis	14 (12)
Focal glomerulosclerosis	8 (7)
Haemolytic uraemic syndrome	7 (6)
Undifferentiated glomerulonephritis	3 (3)
Reflux nephropathy	3 (3)
Other renal diseases	7 (6)

(52%) children. Young children weighing less than 20 kg and children with acute renal failure, who made up 46 (47%) children, received a standard Quinton Scribner Silastic arteriovenous shunt in the leg. One child had a Shaldon catheter inserted through the femoral vein for a week while waiting for a kidney from his mother.

Haemodialysis was performed in the hospital except in one case. It was carried out two or three times a week and lasted between three and six hours. The mean (SD) duration of dialysis was 14.5 (3.2) hours a week. Appropriately sized dialysis plates made by Gambro (Mini Minor, Minor, and Lundia) and hollow fibres made by Asahi (AM 06, and 09), were used for the first treatment. Special paediatric systems were used for small children to

keep the extracorporeal volume below 10% of the blood volume. For later haemodialysis, machines were used that had dialysate containing acetate: the National Kidney Centre (Fairholme Gardens, London, UK), the HC 103 (Braun, Melsungen, West Germany), and the AK10 (Gambro, Lund, Sweden). The flow rate of the dialysate was standardised at 500 ml/minute or 600 ml/minute depending on which machine was used. The water was obtained from a central deioniser. The final concentration of calcium was 2 mmol/l and of sodium 140 mmol/l. The dose of heparin given was 100 U/kg body weight; 1000 U were given initially as a bolus, and the rest as a continuous infusion. Glucose (10 g/dl) was given to minimise dysequilibrium.

Continuous ambulatory peritoneal dialysis was introduced here in 1984. A Tenckhoff double cuffed peritoneal catheter was inserted surgically. Commercial dialysis solutions in 0.5–2.0 litre bags (Fresenius, Homburg, West Germany) were exchanged four times a day. The volume used was 40 ml/kg body weight for each exchange.¹²

Each patient's biochemical and haematological state was monitored by measuring concentrations of sodium, potassium, urea, creatinine, and haemoglobin in the blood, the packed cell volume, the white blood count, and the platelet count, each once a week. Phosphate and calcium concentrations, and alkaline phosphatase activity were measured once a month, and an x-ray picture of the wrist was taken once a year. All patients were given phosphate binders (aluminium hydroxide, calcium carbonate) and vitamin D. Packed red cells were transfused when the haemoglobin concentration fell below 50 g/l. A relatively normal diet was encouraged, though water and potassium were restricted.

RENAL TRANSPLANTATION

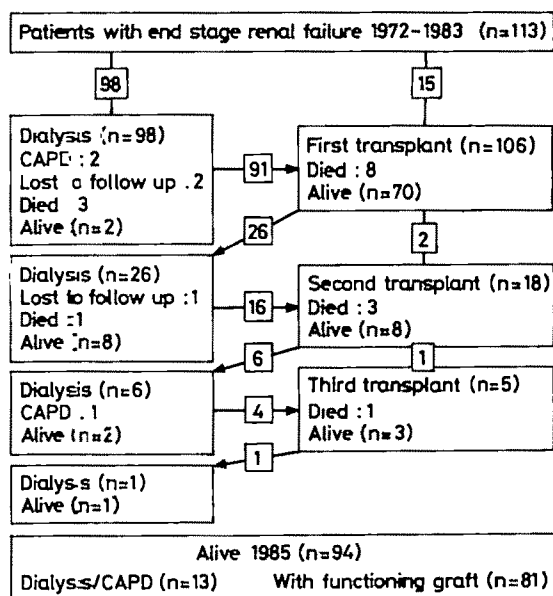
Human leucocyte antigen (HLA) matching and cytotoxic cross matching were carried out for all patients.¹³ Since 1976 all children have received at least three transfusions of packed red cells before transplantations. A negative cross match and ABO compatibility were the only criteria for the first transplantation. Most kidneys were transplanted retroperitoneally into the iliac fossa.¹⁴ Bilateral nephrectomy before transplantation was usually performed only if the kidneys were infected, but four children developed severe hypertension after transplantation and also required nephrectomy. Implantation of the ureters into an ileal loop was necessary in three children with obstructive disease. The immunosuppressive treatment comprised azathioprine and prednisone until 1982 (99 transplantations). Since then, cyclosporin A together

with low doses of prednisolone have been used as previously described (30 transplantations).¹⁵ Children stayed in hospital for six weeks after an uncomplicated renal transplant.

Rejection episodes, diagnosed by a rise in serum creatinine concentration, fever, hypertension, a decrease in urine output, and renal scintigraphy, were treated with intravenous prednisolone 30 mg/kg for three to six days until 1979, and since then with 10 mg/kg. Additionally local radiation of the graft was performed between 1972 and 1979. Antilymphocyte globulin (15 mg/kg) was given between 1977 and 1979 for the first two weeks after transplantation, but this did not reduce the number of episodes of rejection.¹⁶ More recently antithymocyte globulin (5 mg/kg) has been given for five days if vascular rejection was diagnosed.

Results

In December 1985, 94 of the 113 children (83%) with end stage renal failure who entered the treatment programme were alive, 81 (72%) with a functioning graft, 11 (10%) receiving haemodialysis, and two (1%) having continuous ambulatory peritoneal dialysis (fig 1). Three patients on haemodialysis were lost to follow up. The actuarial patient survival, therefore, was 81% after 14 years (fig 2).



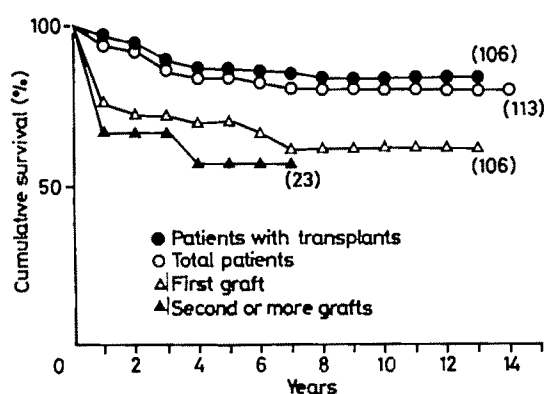


Fig 2 Actuarial survival rates of the 113 children.

Of the 98 patients who entered the programme already receiving haemodialysis the median time spent before they received a transplant was 0.64 years (range 1 day–3.8 years). At the end of 1985 two children had not had transplants but were waiting for suitable donors. One of them started treatment in an adult dialysis unit in 1968 when she was 8 years old, and has been receiving haemodialysis at home for 16.5 years. She has had osteomyelitis and endocarditis and developed 100% cytotoxic antibodies. Three other children were treated with continuous ambulatory peritoneal dialysis after developing cytotoxic antibodies due to multiple blood transfusions while they were receiving haemodialysis. One subsequently received a renal transplant and in one, two transplants were rejected.

One hundred and six patients received 129 renal transplants of which 32 were from living related donors. Eighteen patients received a second graft, and five a third graft. The actuarial survival of all transplanted patients was 83% after 13 years (fig 2). The survival rate of the first graft was 61% after 13 years, and of the second and third graft 57% after seven years. The grafts from living related donors had a 10% better survival rate after five years.¹⁷ The mean observation time of patients with functioning grafts was 4.5 years (range 0.2–12.9).

MORTALITY

Sixteen children (14%) died during the observation period. Nine of the deaths occurred between 1972 and 1976. Four patients died while receiving haemodialysis, a total of one death in 380 patient months. Three of them died after 4, 6, and 23 months, because of gastrointestinal bleeding, hyperkalaemia, and pulmonary oedema, respectively. One child with oxalosis died from cardiac

failure two years after the failure of his first transplant. Twelve patients died after transplantation, eight after the first graft, three after the second, and one after the third, respectively, a total of one death in 424 patient months. Five children died of septicaemia, and three of uraemia after the first graft had failed and further dialysis was refused by the parents. Two children died from intestinal bleeding, one from a perforation by a central venous line during operation, and one of cardiac failure, though the graft was functioning.

MORBIDITY

The morbidity was analysed by adding the number of days spent in hospital during long term dialysis and the number of days spent in hospital after successful transplantation. During the period of dialysis the children were admitted for a mean of 32.3 days a year (range 1–165). The major complications were thrombosis and infection of the arteriovenous fistula (38%). Others were septicaemia (14%), malignant hypertension (6%), and fluid overload (4%). After successful transplantation children were admitted to hospital for an average of 16.9 days (range 0–170) during the first year, which then decreased subsequently to a mean of 3.9 days (range 0.26) after four years. The usual reason for admission was an increased serum creatinine concentration (46%). Other causes were infections (24%), malignant hypertension (11%), osteochondritis dissecans (6%), and surgical complications of the operation (1%).

The mean (SD) haemoglobin and blood urea concentrations and creatinine clearance in patients with chronic renal failure, end stage renal failure, and those who received haemodialysis and successful renal transplantation are shown in table 4. The best rehabilitation was achieved after successful transplantation. During dialysis the average rate of blood transfusion was one unit of packed red cells a month for each patient.

The growth rates expressed as standard deviation scores of height for chronological age as described by Tanner¹⁸ were consistently low even after successful transplantation (fig 3). The mean scores include those of the 16 children with infantile cystinosis who had an extremely poor mean standard deviation scores of -5.3 (1.6). Their mean growth after successful renal transplantation, however, was no less than that of the rest of the patients. On the contrary, standard deviation scores of body weight correlated with actual height increased consistently (fig 3). Hypertension is a major complication of end stage renal failure, and in this retrospective study patients were considered hypertensive only if they were being treated with anti-

Table 4 Mean (SD) concentrations of haemoglobin and blood urea, and creatinine clearance at different stages of treatment for renal failure during the 14 year period

Stage of treatment	No of patients	Haemoglobin (g/l)	Blood urea (mmol/l)	Creatinine clearance (ml/minute/1.73 m ²)
Chronic renal failure (not receiving dialysis)	65	103 (17)	16.8 (10.3)	26.4 (5.4)
End stage renal failure (not receiving dialysis)	98	66 (11)	46.1 (12.8)	4.7 (1.1)
End stage renal failure (receiving dialysis)	85	66 (8)	28.6 (5.7)	—
Six weeks after transplant	80	103 (16)	9.0 (6.0)	72.6 (32.5)
One year after transplant	73	128 (15)	8.8 (5.2)	64.6 (27.4)
Two years after transplant	59	133 (17)	7.7 (4.2)	64.5 (24.2)
Three years after transplant	47	134 (17)	7.7 (5.1)	64.4 (24.2)
Four years after transplant	41	135 (22)	7.9 (6.5)	63.9 (21.5)
Total No. with functioning grafts in 1985	81	122 (26)	11.5 (8.0)	48.4 (22.5)

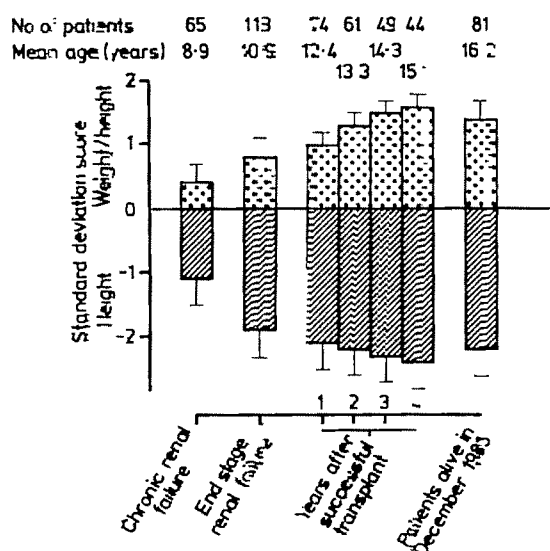


Fig 3 Development of height and weight during the different stages of renal failure expressed as mean (SEM) standard deviation scores.

hypertensive drugs. The incidence of hypertension was highest (77% of patients) four years after transplantation, and lowest (65%) during chronic renal failure.

The overall rate of complications could be assessed in 89 of 94 living patients in 1985 (table 5);

81 had functioning grafts and eight were receiving dialysis. Forty nine patients were receiving conventional immunosuppression with azathioprine and prednisolone, 29 were receiving cyclosporin A, and prednisolone, and three were receiving azathioprine, cyclosporin A and prednisolone. The main complication was hypertension (66%), followed by growth retardation (48%), and Cushingoid appearance (45%). Pubertal development was retarded in 19 of the 61 children (31%) who had entered the pubertal age range. Renal osteopathy was present in 24%, osteochondritis dissecans being the most frequent complication in patients who had had transplants. Cataracts were present in four of 81 patients who had had transplants. Three patients developed liver disease due to azathioprine toxicity in one and haemosiderosis in two. Two required steroid replacement because of adrenal suppression. Of the 30 children treated with cyclosporin A, seven had hypertrichosis and two gingival hyperplasia.

REHABILITATION

Rehabilitation was assessed by the patient's own estimation of state of health, school performance, and occupational performance. In a personal interview 70 of 74 patients (95%) who had had transplants judged their state of health to be good to excellent, but only two of seven patients on dialysis (29%) felt as well as that. Fifty of 52 children of school age who had had transplants were attending school regularly, and two were being taught at

Table 5 Complications in 89 patients being treated for end stage renal failure in December 1985

Complication	No with functioning graft (%) (n=81)	No receiving dialysis (%) (n=8)
Hypertension	57 (64)	2 (2)
Cushingoid appearance	39 (44)	1 (1)
Retardation of growth	38 (43)	5 (6)
Retardation of puberty	15/16 (25)	4/61 (7)
Osteochondritis dissecans	12 (14)	0
Osteodystrophy	1 (1)	8 (9)
Hypertnchosis	7 (8)	0
Cataract	4 (5)	1 (1)
Azathioprine toxicity	1 (1)	0
Haemosiderosis	0	2 (2)
Adrenal insufficiency	1 (1)	1 (1)
Gingival hyperplasia	2 (2)	0

home. Of five school children receiving dialysis, four attended school part time and one was taught at home. The mean delay in school education was one year (range -3 to +1) compared with the appropriate grade for age of the healthy child population. Twenty one of 25 adult patients who had had transplants (84%) had full time jobs, but only two of five patients receiving dialysis did so. Six patients were unemployed but able to work (four with functioning grafts and two receiving dialysis).

Discussion

The outlook for children with end stage renal failure has improved remarkably in the last 20 years,⁸ and regular dialysis and renal transplantation are now both acceptable methods of treatment.^{4, 5} In 14 years at our centre we have treated 113 children with end stage renal failure. The mean time receiving dialysis while waiting for a transplant was 0.6 years, which is shorter than waiting times reported from other centres.^{9, 10} For this reason only four patients received dialysis at home solely because of the long waiting time.

Anaemia was a serious problem during dialysis with a transfusion rate of 1.0 units of packed red cells each month; this is similar to the 1.2 units a month reported by Trachtman *et al.*⁹ Multiple blood transfusions occasionally caused iron overload and the development of cytotoxic antibodies with the consequent delay in renal transplantation. Fortunately hepatitis B infection did not occur. Uraemia was well controlled during dialysis, as shown by the results of laboratory tests (table 4).

A fully integrated service of dialysis and transplantation permitted the optimal treatment at any time. In such a system, particularly when living

related donors were available, renal transplantation without prior dialysis was possible in 15 children. The high proportion of living related donors (25%) reflects our conviction that renal transplantation is the most effective treatment and should be offered early to children with end stage renal failure; this is confirmed by Fine¹⁹ and Chantler.¹⁰ The main advantage of using living related donors is the short period of end stage renal failure.

The overall survival rate of the children was 81% after 14 years, which is comparable with other large series.¹⁰ The mortality of 14% included cases from the early learning period when the dialysis unit was being built up, and after transplantation when too much immunosuppressive treatment led to lethal septic complications. During the last 10 years only seven patients died, comparing favourably with the mortality of 9% reported by Trachtman.⁹

The morbidity was considerable in both patients who received dialysis and patients who had transplants. Hospital admissions lasted for an average of 32.2 days a year during dialysis, and for 16.9 days during the first year after transplantation. Later on the average stay decreased to 3.9 days after four years.

Growth is nearly always impaired in children with chronic renal failure.^{20, 21} The short stature is already obvious by the time renal function is reduced to 25%, and becomes even more so after successful renal transplantation. The retardation of growth observed in our series may be worse than in other series because ours included a high percentage of patients with cystinosis (10%). Their development after transplant, however, was not different from the group as a whole. None of our patients was malnourished as shown by standard deviation scores of weight correlated to actual height. Other factors, therefore, such as renal osteodystrophy, and steroid dosage seem to be responsible for retardation of growth. More normal growth after renal transplantation was recently reported, however, when treatment with cyclosporin A had been given, which permitted lower doses of steroids to be used.^{22, 23} Sexual development was unfortunately not adequately documented in our cases, and so only the pubertal stages during the clinical evaluation in 1985 were investigated. At that time 19 of 61 patients of pubertal age showed pubertal retardation, which is consistent with other reports.^{10, 24}

Hypertension is another common complication of end stage renal failure that threatens long term prognosis. In our review the incidence of hypertension varied from 65% in chronic renal failure to 77% four years after renal transplantation. One patient with a functioning graft died from hypertensive cardiac failure. The underlying disease and

fluid overload are common causes of hypertension during dialysis.²⁵ After renal transplantation, steroids dosage and renal artery stenosis are major causes.²⁶

Rehabilitation as measured by school attendance and full time employment was excellent after successful transplantation. Most patients judged their own state of health to be good or excellent. We hope that steroid induced complications will become less common in the future as the use of cyclosporin A increases, allowing a major reduction in the use of steroids. Nevertheless, new problems such as nephrotoxicity from cyclosporin A have yet to be solved.²⁷

The management of children with end stage renal failure and their families comprises a complex regimen of dialysis, hospital admission medication, nutrition, and operations. It requires a sympathetic staff of paediatric nephrologists, nurses, dietitians, teachers, social workers, and psychologists. Their strenuous efforts will be rewarded by the high rate of full rehabilitation of children who otherwise would not survive.

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Effect of supine posture on peak expiratory flow rates in asthma

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SUMMARY In order to determine the effect of supine posture alone on the peak expiratory flow rate (PEFR) in children with asthma, 22 children with asthma of varying severity had PEFR readings taken in the standing position and subsequently at 30 minute intervals in the supine position for a period of up to four hours. In order to minimise any stress factors no other procedures—for example, taking of blood specimens—were performed during the duration of the tests, which were carried out in a relatively dust free room with no curtains and minimal furniture. Fifteen non-asthmatic children acted as controls. The results showed a significant drop in the PEFR readings in the supine position in asthmatic children compared with the controls; this reverted back to baseline levels on assuming an upright posture at the end of the test without any medication. It is concluded that airflow obstruction can be induced by supine posture per se in asthmatic children; this may be a major factor contributing to nocturnal wheeze or cough.

Nocturnal cough or wheezing is a prominent feature of childhood asthma and has generally been attributed, among other factors, to the nadir in endogenous corticosteroid concentrations normally found in the early hours of the morning.^{1 2} The effect of the supine posture alone on the calibre of the airways has received but scant attention,^{3 4} and, to the best of the author's knowledge information on this regarding asthmatic children is lacking in the English language literature. This study, the first of its kind in children, was carried out to see whether the supine posture on its own had an effect on the peak expiratory flow rates (PEFR) in normal (non-asthmatic) and asthmatic children.

Patients and methods

Twenty two known asthmatic children, ranging in age from 4 years 10 months to 11 years 10 months (mean 8 years 6 months) were studied. There were 16 boys and six girls who were all regular attenders at the paediatric outpatient asthma clinic and were adept at using the Wright Mini peak flow meter. Duration of the asthma was from one to 10 years. Eleven children complained of nocturnal cough or wheeze during the six month period preceding the tests, five had had nocturnal symptoms in the past but were free from these at the time of the tests, and six had had no nocturnal symptoms at any time. Six

children were maintained on β_2 -agonists alone ('mild' group), nine on a β_2 -agonist plus sodium cromoglycate or theophylline, or both ('moderate' group), and the remaining seven on a bronchodilator plus corticosteroids ('severe' group). All but one child were well controlled at the time of the study, and all were free from infection of the upper and lower respiratory tract.

All children were instructed not to take any medication on the morning of the tests. They were investigated between 0730 and 1300 hours as follows: after reporting to the clinic at approximately 0730 hours, each child was instructed to empty the bladder to ensure that the need to micturate would not subsequently interfere with the test; the PEFR was measured with the patient in the standing position, the best of three results being taken as the accepted baseline reading. The patient was then placed in the supine position on an examination couch with no pillow, and serial PEFR readings were taken at 30 minute intervals up to four hours with the patient remaining supine all the time, after which three further readings were taken in the standing position immediately on standing up and at 30 and 60 minutes after assuming the upright posture. Informed parental consent was obtained in each case. In order to minimise any possible stress no other procedures, such as venepuncture for taking of blood specimens, were carried out any

Table Mean (SEM) changes in peak expiratory flow rate (PEFR) with alterations in posture expressed as percentage of

	Height (cm)	Expected PEFR	Standing PEFR	Supine			
				30 minutes	1 hour	1½ hours	2 hours
Control patients (n=15)	130.1 (2.4)	263.0 (12.5)	258.7 (9.5)	-4.3 (2.1)	-4.3 (1.4)	-4.1 (1.1)	-4.9 (2.1)
Patients with asthma (n=22)	127.4 (2.4)	248.5 (12.7)	223.2 (13.6)	-17.3 (2.6)	-19.0 (2.4)	-19.0 (2.6)	-20.3 (2.6)
p value				<0.001	<0.001	<0.001	<0.001

time on the morning of the tests. These were done in a clean, relatively dust free clinic room with no curtains and minimal furniture. Fifteen non-asthmatic children acted as controls (mean age: 8 years 8 months; range 5 years 5 months to 11 years 7 months). During the initial few weeks of the project the examination couch was covered with a clean cotton sheet during the tests (10 asthmatics, six controls); clean plastic sheeting was substituted during the remainder of the study period to eliminate any possible allergic factors that could have conceivably influenced the results (12 asthmatics, nine controls).

Statistical analysis was done using the Mann-Whitney U test. All the results were expressed as percentages of the expected PEFR values and quoted as mean (SEM).

Results

All the asthmatic patients showed a significant drop in the PEFR in the supine position compared with the controls (fig 1). The table shows the drop in PEFR's in the supine position expressed as percentages of the expected value: after 30 minutes in the supine position, there was a 17.3 (2.6)% drop in the mean PEFR, compared with a 4.3 (2.1)% drop in the controls ($p < 0.001$). This difference was maintained throughout the four hour period in the supine posture.

Immediately on standing up the mean PEFR rose in both controls and children with asthma, and 30 minutes after standing the difference between the two groups was no longer significant; however, as the table shows, the children with asthma were not quite back to baseline by one hour after getting up.

When the 10 children with asthma lying on cotton sheets were compared with the 12 lying on plastic the mean falls in PEFR (% of expected) were 17.94 (3.86) and 16.69 (3.7)%, this was not significant. Similar results were obtained for values at the various 30 minute intervals when the children were lying down as well as for those after resuming the

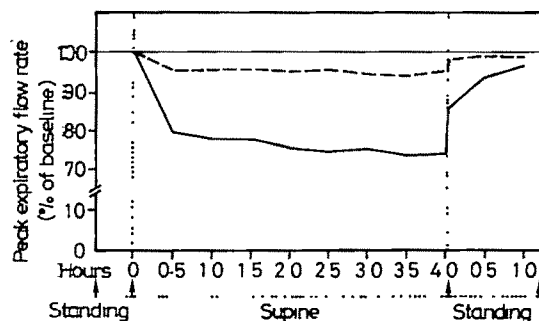


Fig 1 Percentage changes in mean peak expiratory flow rates from standing to supine position in patients with asthma (—) and controls (---)

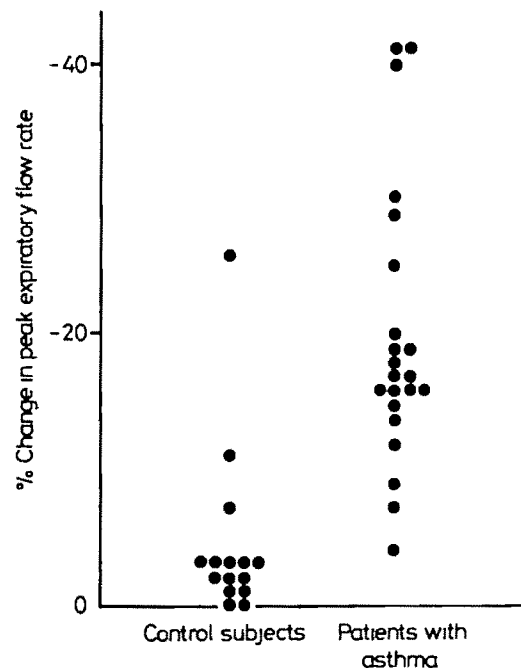


Fig 2 Mean change in peak expiratory flow rate (as % of expected) measured in patients between 30 minutes and four hours in the supine position.

expected values (overall results)

Supine				Standing		
2½ hours	3 hours	3½ hours	4 hours	Immediately on standing	30 minutes	1 hour
-4.1 (1.9)	-5.0 (1.9)	-5.6 (2.0)	-4.2 (1.9)	-1.7 (1.4)	-0.8 (0.6)	-0.8 (0.6)
-21.1 (2.1) <0.001	-20.7 (2.1) <0.001	-21.8 (2.5) <0.001	-21.3 (2.5) <0.001	-11.0 (1.9) <0.001	-4.9 (1.6) NS	-2.1 (1.0) NS

NS=Not significant

standing position—that is, there was no significant difference ($p > 0.05$) between the subjects lying on cotton or on plastic sheets, whether they were asthmatic or were controls.

The variability of the drop in the PEFR in individual subjects is shown in fig 2 which gives the average of the eight values for each subject when they were lying down. The children with asthma showed a large drop in the PEFR compared with most of the controls; there was one control who showed a large fall in the PEFR.

Discussion

Various mechanisms have been put forward as contributing to nocturnal symptoms in people with asthma: circadian troughs (bathypnase) in plasma cortisol,^{1,2} adrenaline,^{2,5} and cyclic AMP concentration,² circadian variation in autonomic nervous tone, mediator release, nocturnal airway cooling, exposure to house dust mite antigen, decreased mucociliary clearance at night, gastro-oesophageal reflux with reflex bronchoconstriction, and possibly sleep. By using a peak flow meter, a normal rhythm in airway calibre has been shown to occur in non-asthmatics, in whom an amplitude (peak to trough) of the PEFR rhythm is mean (SD) 8.3 (5.2)%, the trough occurring in the early hours of the morning.⁶ People with asthma show an identical rhythm but with an exaggerated amplitude (50.9% greater in adults,⁷ 22.6% in children⁸); this suggests an exaggeration of the normal PEFR rhythm caused by increased bronchial lability. The present study examined the effect of posture per se on airway obstruction, and was carried out during the daytime with the subjects being awake so that there were no changes that could be caused by diurnal variation and there was no disruption of the normal daily

shifts. As these mechanisms would be operational at night none of them could account for the fall in PEFR in the supine position in our patients. The return to normal or near normal PEFR values on reassuming the upright posture, without any medication, clearly shows that the fall in PEFR was in fact due to the supine posture itself. This may have therapeutic implications: drug treatment is of limited value in the management of nocturnal symptoms of asthma,⁹ but propping a child up in bed may be beneficial. A therapeutic trial in this connection is currently in progress.

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Adolescent growth and pubertal progression in the Silver-Russell syndrome

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SUMMARY The pattern of growth and development of 18 adolescent children with the Silver-Russell syndrome was studied. Mature height was about -3.6 standard deviation scores in both sexes. This is comparable to the height reduction at diagnosis, which has been reported previously. The pattern of puberty and adolescent growth was essentially normal and occurred at a marginally earlier time than normal, although in this small series the differences were not significant. In the girls there was a tendency to gain subcutaneous fat after puberty. This trend was not apparent in the boys.

Of the recognisable growth disorders presented to the paediatrician one of the more common is the Silver-Russell syndrome. The characteristic physical features of this syndrome were described independently but almost simultaneously.^{1,2} Such patients are usually thin, with short stature noticeable from birth. There are a number of dysmorphic features such as a small and triangular face, lowset ears, and clinodactyly.

The work of Tanner *et al.*³ described in detail the natural history of growth in this disorder. As these authors stated, however, few of their patients had reached maturity and thus a quantitative description of the later stages of longitudinal growth was not possible. Since that time a number of the patients have reached physical maturity, and sufficient auxological data have been collected to allow a longitudinal analysis of physical growth in this syndrome.

Methods

The criteria adopted by Tanner *et al.*³ for the diagnosis of Silver-Russell syndrome were: (a) stature that was two standard deviations below the 50th centile for height on British standards; (b) birth weight when adjusted for sex, length of gestation, birth order, and maternal height two standard deviations or more below the 50th centile on the Tanner-Thomson standards⁴; and (c) absence of any other recognisable syndrome, and of chromosomal, endocrine, metabolic, chondrodysplastic, or psychiatric disturbances that would account for the short stature.

The clinical records and existing growth data of the patients who had satisfied those criteria were reviewed. The original diagnosis of Silver-Russell syndrome was reassessed. In addition to the criteria adopted by Tanner *et al.*,³ patients had to exhibit the classical features of this syndrome—for example, clinodactyly, a triangular face, and lowset ears.⁵ Patients to be included in this study were then selected by virtue of firstly, having stopped growing in the sense that they had grown less than 1 cm in the last year of measurement and secondly, that their growth had been measured for at least three years before the onset of puberty. These selection criteria yielded a total of 18 patients, nine of each sex.

Using the longitudinal growth data produced from these patients it was possible to describe the mean growth curve of a number of linear dimensions such as height and sitting height. The growth curves of such dimensions have a characteristic and similar shape in normal individuals. When attempting to describe the 'typical' or 'mean' growth curve of a specific group of individuals, however, account must be taken of the variability in timing, duration, and intensity of biological events; in particular the adolescent growth spurt. If this variation in the tempo of growth is not accommodated the growth curve found by simply taking the mean of individuals' measurements at different ages will not be representative of the true mean curve. In such a growth curve the duration of the adolescent growth spurt is lengthened and its intensity reduced.

In the study reported here, as we wished to study specifically the growth period around puberty, special attention was paid to this phase-effect. In the

past this problem has been overcome by centering individual growth curves on discernable common events notably the age at peak height velocity (PHV). An alternative approach is to apply a mathematical model to the individual growth curves and use the mean values of the mathematical parameters that describe the individual curves to produce a mean constant curve.⁶

The growth curve for many anthropometric variables can be defined by the model described by Preece and Baines that used five parameters, each being associated with meaningful biological events.⁷ This mathematical model is:

$$h = h_1 - \frac{2(h_1 - h_0)}{\exp[s_0(t - \theta)] + \exp[s_1(t - \theta)]}$$

where h is height at age t , h_1 is final or adult height, s_0 and s_1 are rate constants, θ is a time constant, and h_0 is height at age $=\theta$. It is an improvement on previous models that only considered parts of the growth curve^{8,9} or produced many, sometimes biologically meaningless, parameters.¹⁰ This method of growth modelling was applied to the longitudinal data of each child for stature, sitting height, and subischial leg length.

Table 1 *Biological parameters derived from the Preece-Baines curves pertaining to stature*

	Boys Mean (SD)	Girls Mean (SD)
Adult height (cm)	150.7 (2.8)	142.0 (6.2)
Size at peak height velocity (cm)	135.7 (3.2)	127.5 (5.5)
Age at peak height velocity (years)	13.6 (1.0)	11.6 (1.4)
Velocity at peak height velocity (cm/year)	8.3 (1.5)	8.0 (1.4)

A constant component of the Silver-Russell syndrome is that patients are thin, with skinfold thicknesses being appreciably below normal. By the nature of their growth curves measurements of skinfolds do not easily lend themselves to curve fitting. In order to describe the changes in these measurements that occur throughout growth, standard deviation scores (SDS) were calculated for the skinfold measurements at the triceps and subscapular sites, allowing for age and sex differences. These scores were determined by: $SDS = (X - \bar{x})/Sx$ where at the age in question, X is the measurement, $\bar{x}$ is the mean of the measurement, and Sx is the standard

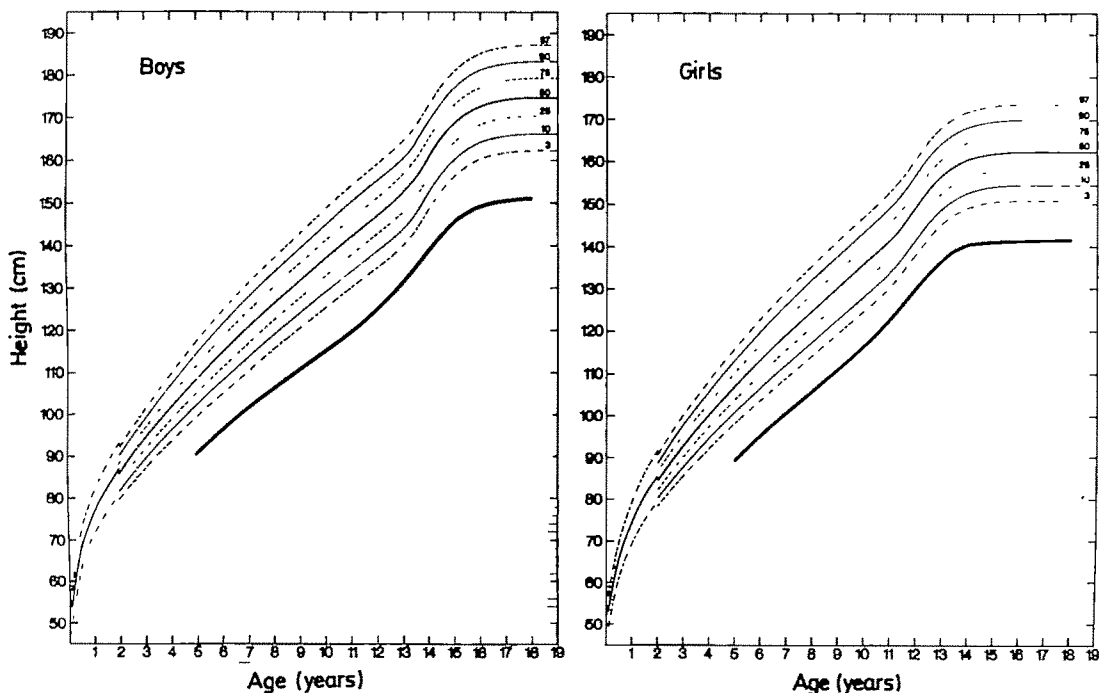


Fig 1 Mean constant curves for height attained in boys and girls plotted on British standards

deviation of the measurement. The standardising data were taken from the data of Tanner and Whitehouse.¹¹ Standard deviation scores for both skinfold sites were calculated from the data existing closest to three years before the age at PHV, at age of PHV, and three years after this event.

A disturbance of puberty events has been cited as occurring in some cases of Silver-Russell syndrome.¹ To obtain some indication of the pattern of development of sexual characteristics for the children in this study the ages of attainment of puberty stages were recorded for each child.¹²

Results

Table 1 shows the means and standard deviations of some of the biological parameters derived from the Preece-Baines curve, which were obtained from the individual fits to the stature data of the boys and girls.

In both sexes adult height was well below the third centile for normal British children. Indeed, the standard deviation scores of adult height for boys and girls was -3.61 and -3.58 , respectively. Fig 1 shows the mean constant curves for stature for both sexes. Fig 2 shows the height velocity curves derived

from these and plotted on standards for normal British children.

Table 2 shows the derived biological parameters for sitting height and subischial leg length for both sexes. Adult sitting height was -3.29 standard

Table 2 *Biological parameters derived from the Preece-Baines curves pertaining to sitting height and subischial leg length*

	Boys Mean (SD)	Girls Mean (SD)
<i>Sitting height</i>		
Adult sitting height (cm)	82.7 (1.6)	78.2 (3.0)
Size at peak sitting height velocity (cm)	74.3 (1.4)	70.9 (2.8)
Age at peak sitting height velocity (years)	14.0 (1.0)	12.2 (1.6)
Velocity at peak sitting height velocity (cm/year)	5.1 (1.0)	3.9 (0.9)
<i>Subischial leg length</i>		
Adult subischial length (cm)	68.4 (2.2)	64.2 (4.5)
Size at peak leg length velocity (cm)	61.4 (2.0)	57.3 (3.7)
Age at peak leg length velocity (years)	13.0 (0.9)	11.0 (1.1)
Velocity at peak leg length velocity (cm/year)	4.7 (1.3)	4.3 (0.6)

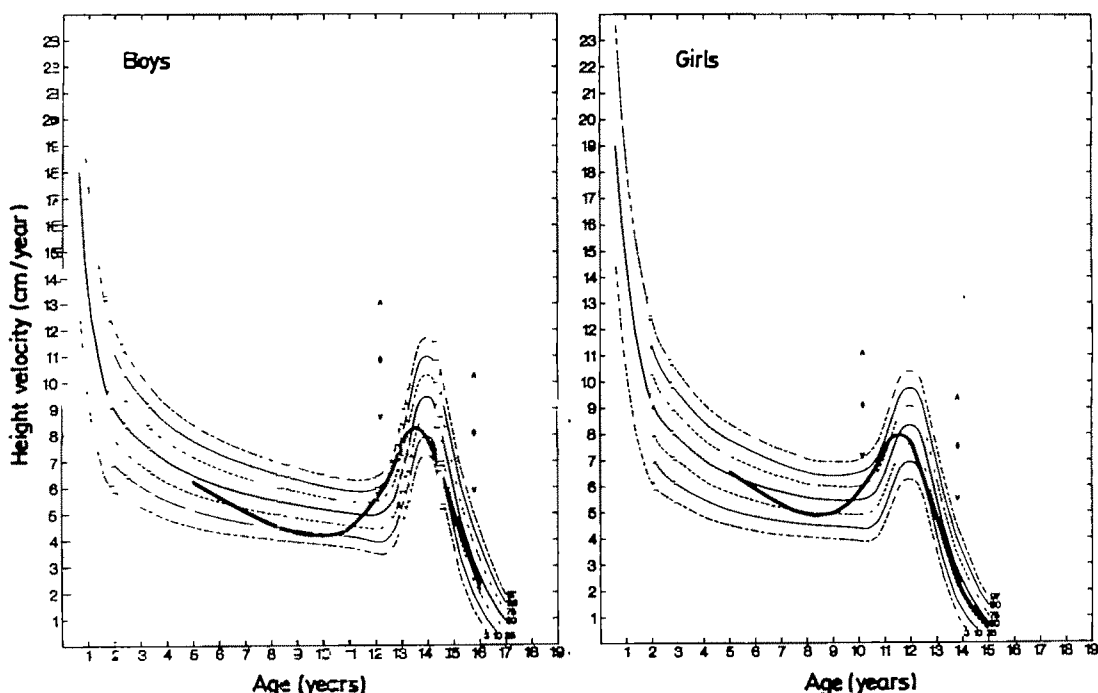


Fig 2 *Mean constant curves for height velocity in boys and girls plotted on British standards*

deviation scores below the mean in the boys and -3.08 for the girls. Adult subischial leg length was -3.06 standard deviation scores below the mean in the boys and -2.64 below the mean in the girls.

The mean values of the standard deviation scores at the triceps and subscapular skinfold sites in both sexes are shown in table 3. In all but one case the mean skinfold standard deviation score is below the average for normal British children.

Mean age of attainment for each stage of pubertal development and mean age of menarche are shown in table 4. The centile position of these ages as compared with normal British children is shown in the third column. As would be expected the girls show pubertal changes at a slightly earlier age than the boys.

Table 3 Mean standard deviation scores of two skinfolds (SEM)

	Triceps	Subscapular
<i>Boys</i>		
3 years before peak height velocity	-0.13 (0.17)	-0.03 (0.18)
At peak height velocity	-0.23 (0.24)	-0.04 (0.17)
3 years after peak height velocity	-0.11 (0.25)	-0.09 (0.20)
<i>Girls</i>		
3 years before peak height velocity	-0.50 (0.17)	-0.25 (0.14)
At peak height velocity	-0.33 (0.20)	-0.15 (0.18)
3 years after peak height velocity	-0.13 (0.31)	+0.03 (0.17)

Table 4 Attainment of puberty stages and age of menarche (SEM). The centile position of each age is shown in the third column. Conventionally centile positions below the 50th centile indicate delayed attainment of a puberty stage

Stage	Mean age of attainment	Centile position
<i>Boys</i>		
Pubic hair 2	12.52 (0.35)	~50th
Pubic hair 3	13.58 (0.28)	~50th
Pubic hair 4	14.57 (0.35)	~50th
Genitalia 2	12.58 (0.33)	25th-50th
Genitalia 3	13.68 (0.41)	~25th
Genitalia 4	14.88 (0.45)	10th-25th
<i>Girls</i>		
Pubic hair 2	11.60 (0.46)	~50th
Pubic hair 3	12.51 (0.49)	~50th
Pubic hair 4	13.04 (0.60)	~50th
Breast 2	11.47 (0.61)	~50th
Breast 3	12.61 (0.50)	25th-50th
Breast 4	13.22 (0.66)	~50th
Menarche	12.98 (0.59)	~50th

Discussion

The aim of this work was to describe some of the features of longitudinal growth in the Silver-Russell syndrome. For a number of patients sufficient auxological data have been collected to produce growth curves and to fit a mathematical model to those curves. Therefore, the mean constant curve for a number of body dimensions can be described. Standard deviation scores were calculated for tricep and subscapular skinfold measurements and the age of attainment of puberty stages were also recorded.

The major presenting feature of this syndrome—short stature—affects both sexes to the same degree. The slight difference in the adult height standard deviation scores between boys and girls is not significant ($p>0.05$). The mean height standard deviation score at referral found by Tanner *et al*³ was -3.58 , remarkably similar to the reduced adult height found in this study. This indicates that there is little catch up growth in the Silver-Russell syndrome during childhood and adolescence. It may also confirm the observation of Tanner *et al*³ that growth essentially proceeds normally in childhood; the patient, however, always remains small in comparison with his or her peers. In contrast to this it has been reported in a recent publication that five out of 15 patients diagnosed as having Silver-Russell syndrome experienced catch up growth.¹³ It should be noted, however, that a number of the patients described by these workers would not have satisfied the diagnostic criteria adopted in our study.

The Preece-Baines curve produces a number of biological parameters pertaining to the adolescent growth spurt. An abnormal pattern and timing of pubertal events was originally reported by Silver *et al* as one of the features of the syndrome.¹ Age at PHV in both sexes was about six months earlier than for normal British children. Nevertheless, as the standard deviation of the timing of this event is about 0.9 of a year in both sexes,^{14 15} the age at PHV found in this work is well within normal limits. The actual velocity of growth at this time, 8.3 cm/year in the boys and 8.0 cm/year in the girls, is also well within normal expectations, although slightly below the mean velocity found for British children. Other biological parameters derived from the mean constant curve such as the age at take off (the beginning of the adolescent growth spurt) and the velocity at take off are also within normal ranges, although again slightly reduced. Consequently, all these factors tend to indicate an essentially normal adolescent growth spurt that is reduced slightly in magnitude and occurs slightly early. This description of the adolescent growth spurt is supported by the height velocity curves shown in fig 2.

The standard deviation scores for adult sitting height and subischial leg length would suggest that leg length is reduced to a lesser degree than sitting height. This difference, however, is not significant at the 5% level and therefore we cannot conclude that adults with Silver-Russell syndrome are disproportionate. In normal British children leg length reaches its peak velocity on average about six months earlier than the trunk. Also, the spurt at adolescence in sitting height is greater than in the lower limbs. In the group of children included in this study peak leg length velocity is roughly one year in advance of peak sitting height velocity. This difference is significant at the 5% level in the boys but not in the girls. The girls have a greater peak velocity in leg length than in sitting height and although the difference between the peak velocities is not significant, this pattern is very similar to that seen in normal adolescents.

The values of the mean standard deviation scores for the triceps and subcapular skinfold measurements shown in table 3 are similar to those reported for the triceps skinfold site alone by Tanner *et al.*³ The mean standard deviation scores are closer to the mean for the normal population in this present group than is usually found in younger children with Silver-Russell syndrome.³ The data presented here support the description that body composition tends to normality in later childhood and adolescence.⁵

The mean age of attainment of puberty stages as shown in table 4 shows that for the group of children in this study the mean ages are similar to those found in normal British children, with the ages lying on or close to the 50th centile. Mean age of menarche in the nine girls studied here is remarkably close to the mean age of 13.0 years usually cited for normal British girls. Age of attainment of genitalia stages 2 to 4 in boys occur progressively later in comparison with normal British children. The 50th centile for time spent between these stages is 1.9 years in normal children,¹⁵ while in this study the time spent between the stages was 2.3 years. Nevertheless, this value is still within the normal range. Thus we must conclude that there is a normal pubertal development of sexual characteristics in this syndrome. The belief that there is a disturbance of pubertal development in Silver-Russell syndrome stems from early descriptions of the growth disorder. Since that time more information has become available regarding normal variation in timing of pubertal events and it now seems that adolescent development is essentially normal. Nevertheless, there are still contradictory reports in the literature pertaining to the normality of pubertal events. In a recent report a potential relation between intrauterine growth retardation and an early adolescence

has been cited,¹⁶ while the timing of pubertal events has been reported as normal in an equally recent work.¹⁷

It has been postulated that in the Silver-Russell syndrome intrauterine growth retardation results in a reduction in total body cell mass, and that after birth growth proceeds normally with the child always remaining small in comparison with his or her peers. This study would certainly lend support to the normality of physical growth. Puberty occurs essentially normally both in terms of the adolescent growth spurt and the development of sexual characteristics.

The characteristic appearance of many patients with this syndrome aids in diagnosis, however, the prognosis with regard to adult stature is poor. Human growth hormone has been shown to have variable and short term effects on growth velocity, with some patients showing growth acceleration.¹⁸ Further trials over longer periods are now required and any long term benefit can be judged against the data reported here.

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Histology of breast development in early life

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SUMMARY Histological examination of the breasts of 26 infants and young children who died suddenly between the ages of 3 weeks and 2 years was performed. The glands were composed of well formed lobules surrounded by dense interlobular stroma, while within the lobules there was looser connective tissue. The lobules contained ducts, many of which were dilated and contained secretions. Foci of extramedullary haematopoiesis were found, and in the older infants, fat was prominent within the connective tissue of the breast. Myoepithelial cells were regularly present. No sex differences in breast development at this time were noted. Newborn breast development did not regress rapidly after birth and secretory activity continued for many months in both sexes. This study shows that the human mammary gland remains active for many months after birth and may continue to grow and secrete. The findings are not consistent with the current view that breast development in infancy results from stimulation from 'pregnancy hormones.' It is more likely that the infant's own gonadal secretions are responsible.

The human mammary gland has a number of well recognised phases of growth and development. In late pregnancy the fetal breast (in both sexes) is highly developed, and at birth it often secretes milk.¹ Then at puberty the growth of the breast is usually the first sign of secondary sexual development in girls, and at this time gynaecomastia is not uncommon in boys.² The breast reaches its maximal development during pregnancy in preparation for lactation. There is, however, another ill recognised phase of development of the human mammary gland in the first year or two of life long after the influences of pregnancy have been removed. Contrary to what has been stated³ the infant's breast does not regress rapidly after birth. Careful clinical study has shown that it often persists as a firm discrete nodule in many boys and girls during the first year of life and it may be more prominent by the age of 6 months than earlier and it is only later in infancy that the first sex differences in breast size appear: the gland being bigger than in girls.¹ In prematurely born infant girls this phase of development may be even more prominent.⁴ After the first two years the breast bud usually remains small and barely palpable until puberty.

The histological appearances of the breast in the fetus, at birth, in puberty, and pregnancy have been well described,^{5,6} but there are few reports on breast histology in infancy after the immediate newborn period. Also it is likely that the specimens

of breast tissue that were subject to histological examination were from infants who had died in hospital after chronic illnesses. To obtain information on the natural history and histological appearances of the breast in healthy children it was decided to examine the glands of previously well infants and young children who had died suddenly.

Materials and methods

The breast bud and surmounting ellipse of nipple containing skin was excised from a total of 22 cases of sudden infant death at necropsy; the infants were aged 3 weeks to 6 months. Three infants showed evidence of mild tracheobronchitis and no pathological abnormalities were found in the others. Breast tissue from four additional cases taken at necropsy was examined: a 2 month old girl who died from hydrocephalus and acute pyelonephritis, a 5 month old boy with hydrocephalus and pneumonia, an 18 month old boy with peritonitis due to gastric perforation, and a 2 year old girl who died from shock secondary to trauma. After fixation in formal saline and paraffin embedding sections were stained by haematoxylin and eosin and examined.

Results

On gross appearance the breast gland consisted of a subareolar nodule of firm white tissue up to 1 cm in

diameter. No age or sex differences in size were noticed. On histological examination the glands consisted of well formed lobules surrounded by dense interlobular stroma. The lobules contained a number of ducts (fig 1) and the larger ducts seemed to disrupt the lobular pattern. The connective tissue within the lobules was looser and more delicate than elsewhere but in two cases this also was condensed. The definite lobular pattern was rarely absent after the age of 5 weeks. All the breast specimens contained recognisable ducts. Fat was prominent after the first 2 months of age and was invariably of the adult type. Islets of fat cells were often found within the connective tissue of the breast bud.

In the younger infants (aged 3 weeks to 3 months) the ducts were usually large and dilated and often contained secretions (fig 2). In general the dilated ducts had a single lining of flat epithelial cells (active epithelium) and contained secretions. Desquamated cells were usually present in the duct lumen at all ages, but definite secretion was often seen especially in the first three months, and at this time there were often cytoplasmic buds typical of apocrine secretion (fig 3).

After the first months the ducts were usually smaller, had a double lining of cuboidal epithelium (resting epithelium), and contained little secretion. There was, however, great variation—a single lining was seen as late as 6 months of age, and the dilated ducts of a 10 week old girl had a double lining. Also a double lining layer with eosinophilic secretion was seen in some glands from children over the age of 6 months and large dilated ducts, assuming a papillary appearance were present in the glands of one 18 month old boy. Double epithelial layers were more likely to be found in the embryologically more mature ducts in the subareolar areas.

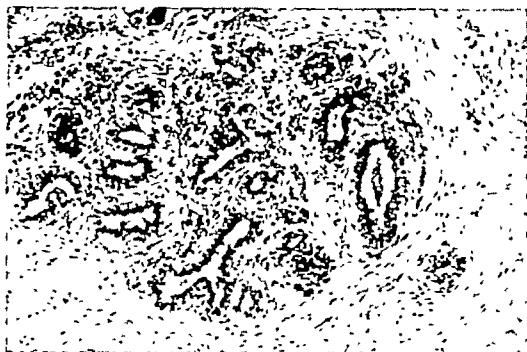


Fig 1 Section of breast of 4 week old girl (sudden infant death) showing the lobular pattern with interlobular and intralobular connective tissue (haematoxylin and eosin $\times 40$).



Fig 2 Large dilated ducts containing plentiful secretion from a 10 week old girl (sudden infant death) (haematoxylin and eosin $\times 80$).

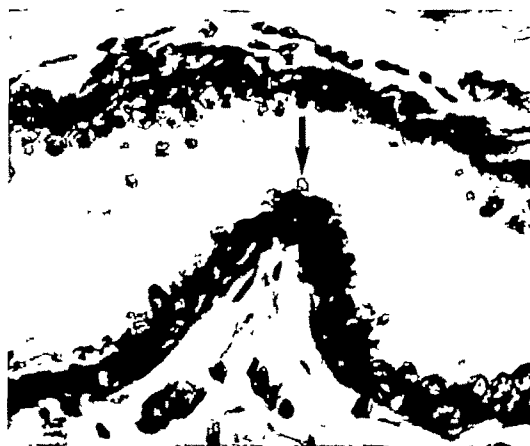


Fig 3 A dilated duct with apocrine secretion showing cytoplasmic globules released in the duct lumen from a 3 week old boy (sudden infant death) Arrow indicates cytoplasmic bud (haematoxylin and eosin $\times 200$).

A cellular infiltrate was often seen within the stroma. Initially this was thought to represent inflammatory change but on more careful examination primitive red and white cells were identified indicating extramedullary haematopoiesis (fig 4). Myoepithelial cells were present at all ages from 4 weeks to 18 months irrespective of whether the gland contained secretion (fig 5).



Fig 4 Extramedullary haematopoiesis in the breast of a 5 week old boy (sudden infant death) Arrow indicates focus of erythroid and myeloid precursors (haematoxylin and eosin $\times 150$)

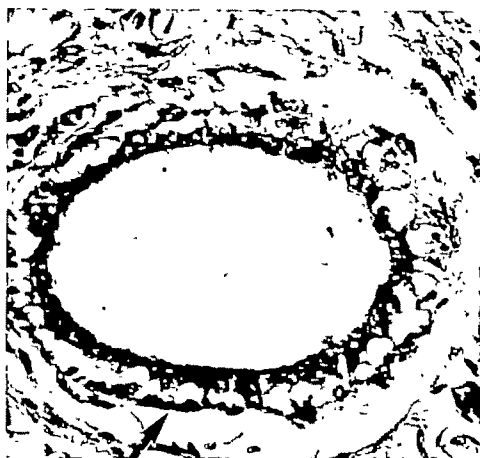


Fig 5 A duct surrounded by a layer of myoepithelial cells (arrow) with clear cytoplasm as seen in the breast of a 2 month old boy (sudden infant death) (haematoxylin and eosin $\times 150$)

Discussion

From this histological study it is clear that the human mammary gland does not involute rapidly after birth but remains active for a few months often showing typical apocrine secretion. In some cases secretion was still seen many months, and once as late as 18 months, after birth. The histological appearances of the lactating breast in early infancy are, in general, similar to the adult puerperal gland,^{5,6} but it has been noted before that in infancy secretion of milk seems to take place in dilated ducts, and definite alveoli at the ends of ducts are

rarely seen.⁷ In general active epithelium was flattened and had a single lining layer while the resting epithelium had a double lining layer. There was, however, great variation. Definite myoepithelial cells were identified at all ages. Extramedullary haematopoiesis in the newborn breast is not a well recognised phenomenon but has been described before and may be a normal feature.⁸

Previous reports have indicated that the breast becomes inactive soon after birth and remains rudimentary during infancy and early life. A recent clinical study, however, has shown that newborn breast development often persisted.¹ There has been little histological study. Pfaltz found that the breast of a 14 month old boy contained a core of connective tissue with 'underdeveloped' parenchyma but also noted that more branching ducts were present in the first three years than later.⁹ Our finding of histological evidence of breast activity (including secretion) after the first months of life is in agreement with that of Tholen who noted some very dilated ducts with a double epithelial layer and lobular pattern in one 8 month old boy.¹⁰ He also concluded that the gland was not smaller in later infancy than earlier as the amount of stroma and especially dense connective tissue had increased. Berka also commented on the increased amount of connective tissue in a 2 year old child.¹¹ We did not notice any difference in the histological appearance between male and female glands and this was surprising as clinical study had shown that after six months breast nodules were absent in boys but often still present in girls.¹ Another surprising finding was the well formed lobular pattern as it had been suggested that lobules are not formed until much later in childhood.⁵ It has been remarked that one of the characteristics of the mature breast is its variability in size and structure¹² and this certainly also applies to the gland in early life.

We know little of the factors that control breast development in infancy and early childhood. Hormones are thought to regulate breast development at puberty, pregnancy, and the puerperium with oestrogen promoting growth of the duct systems and progesterone that of the alveoli.¹³ High circulating concentrations of prolactin are needed for the initiation of milk secretion.¹⁴ It has been suggested that 'pregnancy hormones' may be implicated in postnatal breast development in the infant but this does not seem possible in view of their short half life and it is more likely that the infant's own endocrine system is responsible. Circulating concentrations of follicle stimulating hormone (FSH) rise after birth in both sexes and especially in girls remain relatively high for the next few years.¹⁵ It has been shown that the ovaries of

girls in the first few years of life are quite active with prominent follicular growth and atresia.¹⁶ Plasma oestradiol concentrations are often higher in girls aged 0–4 years than in later prepuberty.¹⁷ The pattern of hormone secretion seems to differ in boys with an early surge in luteinising hormone and testosterone¹⁸ and lower concentrations of FSH and oestradiol than in girls. We did not attempt to make quantitative measurements of breast size. Nevertheless, our failure to find an obvious difference in the sexes in gland size or development was surprising. Also, while it is known that prolactin concentrations are high at birth and in the first few weeks¹⁹ and may be responsible for the initiation of lactation (neonatal milk secretion), the concentrations then decline rapidly to the normal 'non-lactating range'. There may be other factors implicated in milk secretion, however, because in two infants we have seen definite secretion at the ages of 9 and 18 months long after prolactin concentrations might have been expected to have fallen and lactation to have ceased. It might be argued that the features we have observed are the effects of the acute stressful illness associated with the child's sudden death but this does not seem a plausible explanation.

Our study has confirmed that there is a definite phase of breast development in early infancy and early life and we have shown the histological appearances of the gland at this time. Our findings cast some doubt on current views with regard to the role of hormones in breast growth and development. Pregnancy hormones are not likely to be responsible, but the infant's own gonadal secretions (oestrogen, testosterone) are probably important.

We are grateful to Dr W Kealy for his advice and to Miss C Conway and Miss C Forde for typing the manuscript

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Lipoprotein lipase, hepatic lipase, and carnitine in premature infants

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SUMMARY Twenty six preterm infants were studied at the age of 2, 7, and 26 days. The activities of lipoprotein and hepatic lipase in plasma taken 15 minutes after a heparin bolus of 100 IU/kg had been given and the concentrations of carnitine in serum and urine were measured. The mean gestational age was 31 weeks (range 26-35 weeks) and birth weight 1580 g (range 840-2280 g). Thirteen infants weighed under 1500 g at birth (very low birth weight), 20 were of appropriate weight for gestational age and six were small for gestational age. Lipoprotein lipase activity was higher in the preterm infants of appropriate weight than in the infants of very low birth weight and those who were small for gestational age. At the age of 2 or 7 days the activity of lipoprotein lipase in the preterm infants (mean (SEM) 46.2 (4.3) μ mol free fatty acid/ml/hour) was, however, higher than in term infants and adults. Multivariate regression analyses showed that weight and relative birth weight together explained 58% of the variance of lipoprotein lipase activity but only 3% of the variance of hepatic lipase activity. Serum carnitine concentration was lower in the preterm infants than in term infants. Urinary excretion of carnitine increased progressively with age but was independent of serum concentration and carnitine intake. Urinary excretion of total carnitine was significantly greater in the infants who were small for gestational age (mean (SEM) 754 (203) nmol/mg of creatinine, n=6) than in the infants of appropriate weight (161 (22.0) nmol/mg of creatinine, n=12) but acyl/free carnitine ratio was smaller in the infants who were small for gestational age than in infants of appropriate weight (0.56 v 5.5). The results indicate that the slow elimination of fat from the circulation in preterm infants less mature than 32 weeks of gestation can hardly be explained by low lipoprotein lipase activity.

Carbohydrate supply through the placenta ceases after birth, and the glycogen stores of the infant are quickly depleted. Fat from adipose tissue and breast milk then becomes the infant's main source of energy. In very low birthweight infants and in infants small for gestational age adipose tissue depots are limited, and elimination of fat from the circulation is impaired. In addition, fat absorption from breast milk is only 85-90% due to deficiencies in pancreatic lipase and bile salts. Also the intake of breast milk is severely limited by various diseases that are typical of preterm infants. Hence, infants of very low birth weight and those who are small for gestational age may develop energy shortage during their first weeks of life.

Lipoprotein lipase is the rate limiting enzyme for the hydrolysis of triglycerides in plasma lipopro-

teins.¹ In infants, postheparin lipolytic activity (PHLA) has been used as a measure of lipoprotein lipase activity.^{2,3} In preterm infants less mature than 27 weeks of gestation PHLA is less than 30% of the EHLA found in more mature preterm and term infants.²⁻⁴ Our earlier results, however, indicate that lipoprotein lipase activity, measured with a specific method, is higher in preterm than term infants, and as high in term infants as in adults.^{5,6}

Hepatic lipase forms a substantial part of PHLA.⁷ The function of hepatic lipase in triglyceride metabolism is not known for certain.^{1,8} In term and preterm infants the hepatic lipase activities are about three times the lipoprotein lipase activities, and the two lipase activities vary independently.^{5,6} Neither enzyme activity has been systematically studied in infants of very low birth weight and those who are small for gestational age.

Carnitine is essential for the facilitated transport of long chain free fatty acids across the mitochond-

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rial membrane for β oxidation.⁹ Newborn infants may, however, be incapable of sufficient carnitine synthesis.¹⁰ During carnitine free parenteral nutrition or enteral feeding with soybean based formula preterm infants have reduced blood, urinary, and tissue concentrations of carnitine combined with impaired fatty acid oxidation and ketogenesis.¹¹ The adequacy of carnitine intake from breast milk has not been studied in preterm infants.

To investigate the main determinants of fat utilisation in preterm infants we measured the activities of lipoprotein and hepatic lipase in post-heparin plasma and the concentrations of carnitine in plasma and urine of infants of very low birth weight and those who were small for gestational age and of a comparison group consisting of other preterm infants.

Subjects and methods

We studied 26 preterm infants, 12 girls and 14 boys. The purpose of the investigation was explained to the parents and studies were carried out with their consent. The experimental protocol had been approved by the ethical committee at this hospital. Sixteen of the 25 mothers were healthy and had an uncomplicated pregnancy. The gestational ages of the infants ranged from 26 to 35 weeks. Thirteen infants were less mature than 32 weeks of gestation, and three of them weighed more than 1500 g. The birth weights ranged from 840 to 2280 g and the

relative birth weights from -3.2 to $+1.4$ SD units. Relative birth weight refers to the deviation of the individual birth weight from the mean birth weight of the gestational age group divided by the corresponding standard deviation.¹² Twenty infants had an appropriate weight for gestational age (relative birth weight within ± 2.0 SD units) and six infants were small for gestational age (relative birth weight < -2.0 SD units). Thirteen infants had very low birth weight (birth weight < 1500 g): two were more mature than 32 weeks of gestation and four were both small for gestational age and of very low birth weight. Because gestational age is somewhat unreliable we divided the infants into groups according to their birth weights. The table shows the clinical data of the preterm infants.

FEEDING

All infants received pasteurised breast milk from a milk bank, but 20 infants also received 10% glucose intravenously (mean duration 12.5 days). None received fat emulsion or amino acids. The mean amount of breast milk was 34 ml/kg/day (range 0–91) and the mean number of calories 0.17 MJ/kg/day (range 0.10–0.34) during the first three days of life, 159 ml/kg/day (range 31–220) and 0.48 MJ/kg/day (range 0.25–0.62) during 6–8 days of life, and 185 ml/kg/day (range 90–210) and 0.53 MJ/kg/day (range 0.33–0.59) during 25–27 days of life. All infants received supplementation of vitamins A, B12, C, D, and E, and folic acid from the age of

Table Clinical data of preterm infants studied ($n=26$)

	Infants of appropriate weight for gestational age		Infants who were small for gestational age	
	< 1500 g ($n=9$)	> 1500 g ($n=11$)	< 1500 g ($n=4$)	> 1500 g ($n=2$)
Gestational age (weeks) (mean(range))	29.3 (27.4–30.9)	32.6 (29.9–34.6)	30.7 (26.4–34.6)	34.5 (34–35)
Birth weight (g) (mean (range))	1288 (1080–1470)	1941 (1530–2260)	1171 (840–1460)	1820 (1780–1860)
Relative birth weight (SD) (mean (range))	-0.9 (-1.4 to 1.4)	-0.5 (-1.9 to 1.3)	-2.7 (-3.2 to -2.2)	-2.3 (-2.5 to -2.1)
Apgar score < 7 at 1 minute	9	3	4	—
Boys/girls	6/3	6/5	1/3	1/1
No infants who had.				
Mechanical ventilation	9	3	4	—
RDS*/BPD†	9/2	2/—	1/1	—/—
Antibiotic treatment	9	5	3	1
Dopamine infusion	8	—	2	—
Phototherapy (prophylactic)	9	11	3	1
Ductus arteriosus				
Indomethacin treatment	4	—	1	—
Operation	—	—	1	—

*RDS=Respiratory distress syndrome

†BPD=Bronchopulmonary dysplasia

3 days, and iron (3–4 mg/kg/day) from the age of 2 weeks. On average, weight at the age of 7 days was 9% lower than at birth. The mean gain of weight by the age of 26 days was 12.0 g/day (range 2.0–20.0 g/day).

BLOOD AND URINARY SAMPLES

On the 2nd, 7th, and 26th day of life a blood sample was taken through an indwelling peripheral vein catheter for measurement of total and free carnitine and basal plasma activities of lipoprotein and hepatic lipases. On average, the infants had fasted two hours before sampling. On the 2nd day of life a heparin bolus of 100 IU/kg (Medica, Helsinki, Finland) was injected through the catheter of those 11 infants who had reached stable ventila-

tion ($\text{pH} > 7.35$, $\text{pCO}_2 < 6.6$ kPa, $\text{FiO}_2 < 0.45$, $\text{PaO}_2 > 5.9$ kPa) and haemodynamics (mean blood pressure > 45 mm Hg, normal urinary flow, and serum urea nitrogen < 15 mmol/l) and who did not have abdominal distension, intraventricular haemorrhage, or hyperbilirubinaemia. Fifteen minutes after the injection a blood sample was taken for the measurement of lipase activities. At the ages of 7 and 26 days lipase activities were measured for the first time from 14 and one infant and for the second time from six and seven infants, respectively. As we have found previously the infants showed no signs of a tendency to bleed or other side effects as a result of the heparin administration.^{5 6 13 14} Urine was collected for 24 hours between the 1st and 2nd, 7th and 8th, and 26th and 27th days of life. The

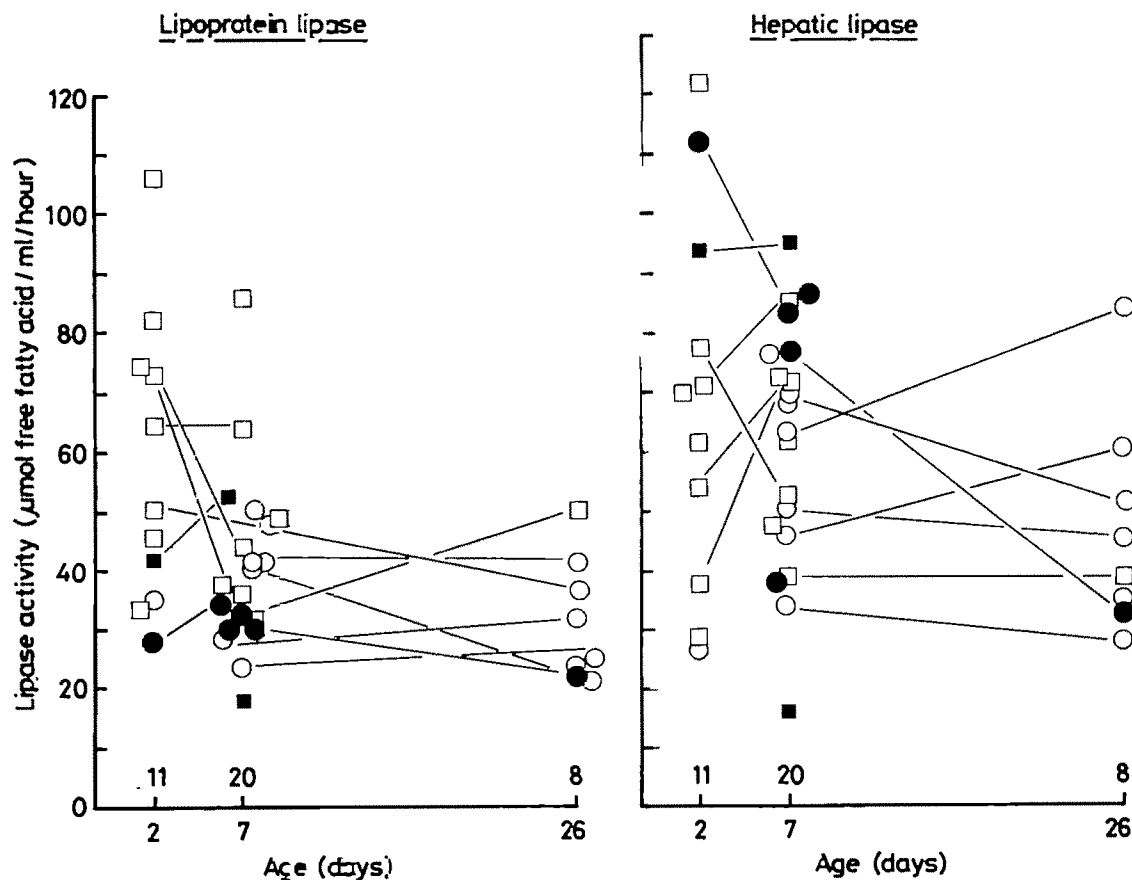


Fig 1 Activities of lipoprotein lipase and hepatic lipase at 2, 7, and 26 days of age. Inset numbers refer to the numbers of subjects. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g. The repeated measurements are connected with lines.

samples were used for the determinations of total and free carnitine concentrations.

BIOCHEMICAL ASSAYS

All blood samples were collected into chilled tubes kept in ice. They were immediately centrifuged, and the plasma and serum obtained were stored at -20°C until assayed within a month. Urine was collected during 24 hours into bottles and kept in a refrigerator. The urinary volumes collected were then measured, and the urinary samples were stored at -20°C until assayed within a month.

Total and free carnitine concentrations were measured with the radioisotopic method of McGarry and Foster¹⁵ modified according to Novak *et al.*¹⁶ Urinary and milk samples were first sonicated, then diluted with 4 volumes of distilled water, and resonicated. Part of the sample was used for the measurement of free carnitine concentration. The rest of the sample was first hydrolysed in 0.1 M potassium hydroxide at 37°C for 60 minutes, and then neutralised and sonicated for the measurement of total carnitine. Urinary carnitine excretion was expressed as nmol/mg of creatinine. Acylcarnitine was calculated by subtracting free carnitine from total carnitine.

Lipoprotein and hepatic lipase activities of post-heparin plasma were measured with the immunochemical method of Huttunen *et al.*⁷: lipoprotein lipase was measured after inactivating hepatic lipase with a specific antiserum produced in rabbits against purified human postheparin plasma hepatic lipase. Hepatic lipase was measured in 1 M sodium chloride, a concentration that inactivates lipoprotein lipase, no serum was added. The substrate was acyl-1- ^{14}C labelled triolein emulsion prepared by sonication.

STATISTICAL ANALYSES

Statistical analyses were performed with the BMDP statistical software package.¹⁷ Two way analyses of variance for the repeated measurements of carnitine were performed with time as a within factor. Wilcoxon test and paired *t* test were used for comparing the repeated measurements of lipase activities. The Mann-Whitney test and unpaired *t* test were used for comparing lipase activities and serum and urinary carnitine concentrations between infants of very low birth weight, those who were small for gestational age, and other preterm infants. In addition, simple linear regression analyses were computed between serum and urinary concentrations of carnitine, lipases, and the other relevant variables. Multivariate regression analyses were then performed to sort out the main factors explaining the variation of lipoprotein lipase activity and carnitine concentration.

Results

POSTHEPARIN PLASMA LIPOPROTEIN AND HEPATIC LIPISE ACTIVITIES

Fig 1 shows lipoprotein and hepatic lipase activities measured at the age of 2, 7, and 26 days. Lipase activities were measured in six infants at 2 and 7 days of age and in seven infants at 7 and 26 days of age. When comparing the repeated measurements the mean activities of both lipases were found to be independent of postnatal age ($p>0.3$).

The activities of lipoprotein and hepatic lipase, measured for the first time at the age of 2 and

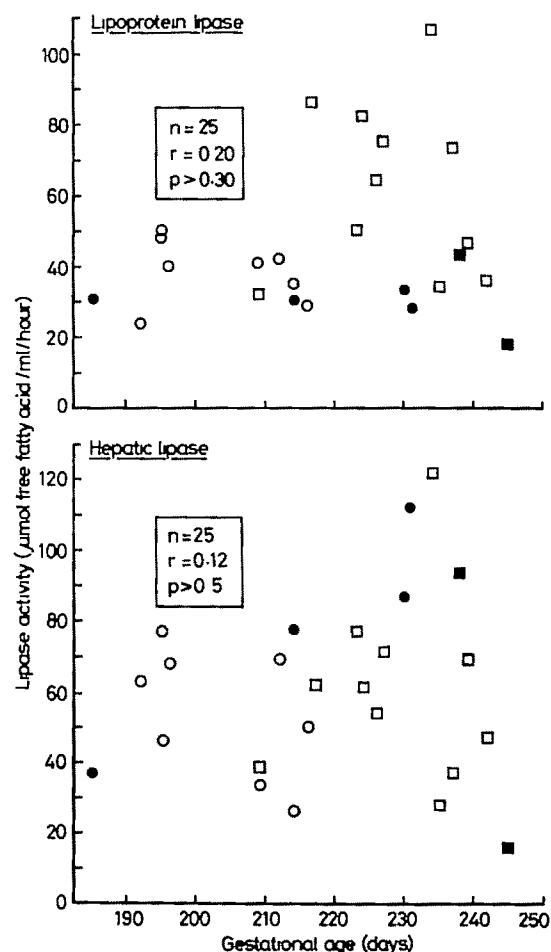


Fig 2 Activities of lipoprotein lipase and hepatic lipase, measured for the first time at 2 or 7 days of age plotted as a function of gestational age. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.

7 days, are plotted as a function of gestational age (fig 2). Both lipase activities were found to be independent of gestational age. Nevertheless, lipoprotein lipase activity correlated positively with birth weight ($r=0.62$, $p<0.001$) and relative birth weight ($r=0.53$, $p<0.001$) (fig 3a). The exclusion of infants who were small for gestational age resulted in a stronger correlation ($r=0.57$, $p<0.001$) between lipoprotein lipase activity and birth weight (fig 3b). Hepatic lipase activity correlated with neither measure.

The multivariate regression analyses showed that birth weight and relative birth weight together explained 58% of the variance of lipoprotein lipase activity but only 3% of the variance of hepatic lipase activity in our preterm infants. When the effects of birth weight and relative birth weight were removed, however, the partial correlation between gestational age and lipoprotein lipase activity (see fig 2 (top)) was -0.57 ($p<0.01$); hepatic lipase remained independent of gestational age.

When the infants who were small for gestational age were excluded, the mean (SEM) lipoprotein lipase activity in the very low birth weight infants (38.6 (3.2) μmol free fatty acid/ml/hour) was lower ($p<0.02$) than in the infants weighing more than 1500 g (62.2 (7.3) μmol free fatty acid/ml/hour) (fig 3b) whereas the mean hepatic lipase activities were similar (54.3 (6.4) μmol free fatty acid/ml/hour for the very low birth weight infants and 60.6 (7.7) μmol free fatty acid/ml/hour for the other infants). Eleven of the 13 infants of very low birth weight studied were less mature than 32 weeks of gestation and 10 of the 13 infants weighing more than 1500 g were more mature than 32 weeks of gestation. Also, the mean (SEM) lipoprotein lipase activity was lower ($p<0.002$) in the infants who were small for gestational age (30.5 (3.2) μmol free fatty acid/ml/hour) than in the infants of appropriate weight (52.3 (5.2) μmol free fatty acid/ml/hour) (fig 3a) whereas the mean hepatic lipase activities were similar (70.7 (15) μmol free fatty acid/ml/hour

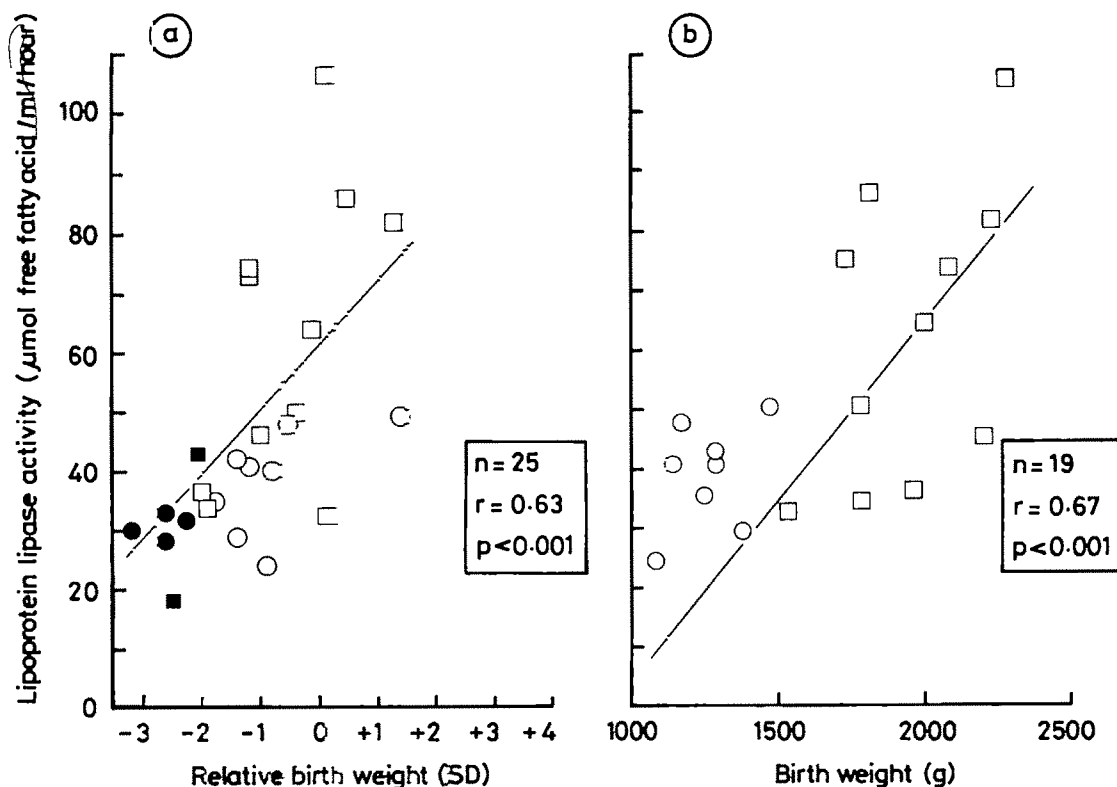


Fig 3 Activity of lipoprotein lipase, measured for the first time at 2 or 7 days of age plotted as a function of relative birth weight (a) and birth weight (b). Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.

for the infants who were small for gestational age and 57.9 (5.2) μmol free fatty acid/ml/hour for the infants of appropriate weight).

SERUM CONCENTRATION AND URINARY EXCRETION OF CARNITINE

Serum total and free carnitine concentrations first decreased ($p < 0.03$) and then increased during the first 26 days of age (fig 4a); the increase was not significant. Urinary excretion of total and free carnitine and acylcarnitine increased ($p < 0.01$) progressively with age from 7 to 26 days (fig 4b).

The multivariate regression analyses showed that urinary excretions of total and free carnitine were independent of the serum concentration of total carnitine and of daily carnitine intake calculated from the ingested milk volume and the concentration of total carnitine (51.6 nmol/ml) in bank breast

milk. Urinary excretion of total and free carnitine, however, correlated negatively with relative birth weight at the age of 2 days ($r = -0.59$, $p < 0.03$ and $r = -0.57$, $p < 0.04$) and 7 days ($r = -0.65$, $p < 0.003$) and $r = -0.61$, $p < 0.006$) but were independent of birth weight and gestational age. Fig 5 shows the negative correlation between total carnitine excretion and relative birth weight at 7 days of age.

At the age of 7 days urinary excretion of total carnitine was larger ($p < 0.001$) in the infants who were small for gestational age (mean (SEM) 754 (203) nmol/mg of creatinine, $n = 6$) than in the infants of appropriate weight (161 (22) nmol/mg of creatinine, $n = 12$) (fig 5). The mean urinary acyl/free carnitine-ratio was 0.56 (range 0.16–1.0) in the infants who were small for gestational age and 5.5 (range 1.5–15) in the infants of appropriate weight. Serum concentrations of total carnitine, however, were not different in the infants who were small for gestational age (mean (SEM) 26.5 (3.5) nmol/ml,

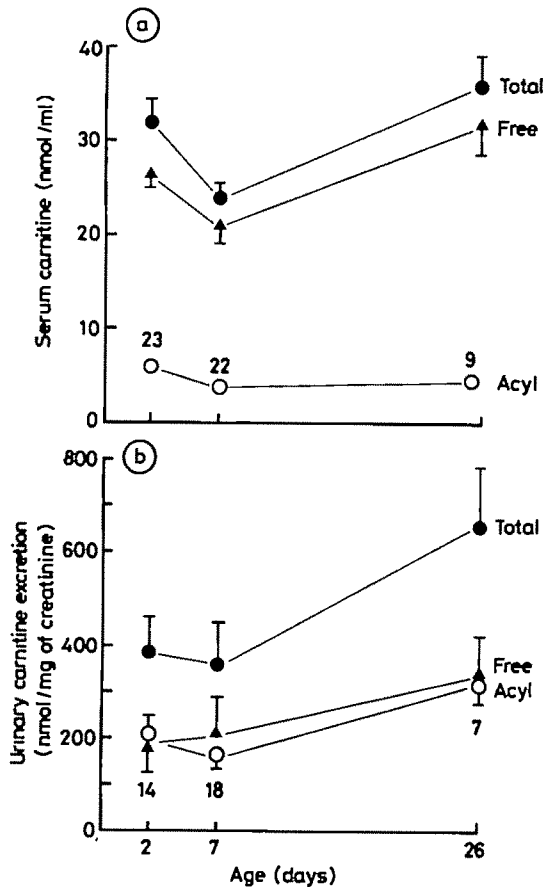


Fig 4 Serum (a) and urinary (b) concentrations of total and free carnitine and acylcarnitine at 2, 7 and 26 days of age. Numbers close to the curves refer to the numbers of subjects

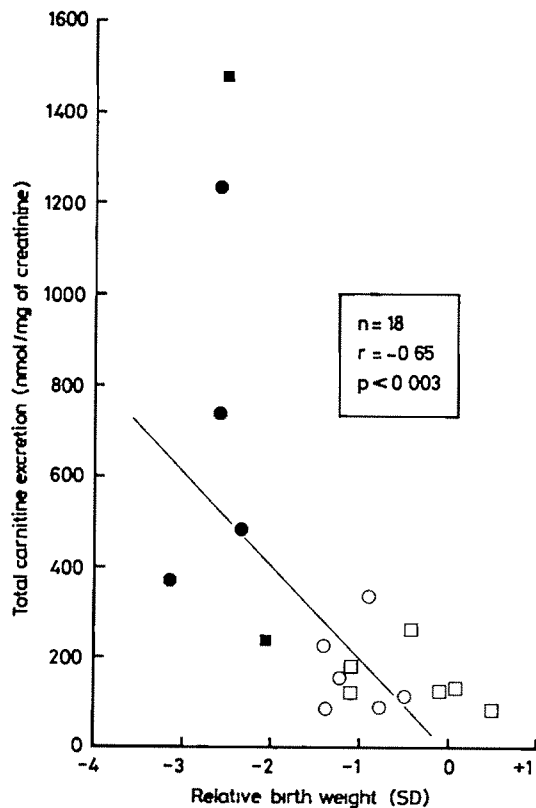


Fig 5 Total carnitine excretion as a function of relative birth weight at 7 days of age. Open symbols refer to the infants of appropriate weight and solid symbols to the infants who were small for gestational age. Squares refer to the infants weighing more than 1500 g and circles to the infants of very low birth weight weighing less than 1500 g.

$n=6$) and those of appropriate weight (22.7 (1.7) nmol/ml, $n=12$).

Discussion

Postheparin lipolytic activity²⁻⁴ and fat elimination tests¹⁸ suggest that lipoprotein lipase activity may be low in preterm infants. We found, however, that the mean (SD) activity of postheparin plasma lipoprotein lipase, measured with a specific method, was appreciably higher in our three groups of preterm infants (46.2 (22.0) μmol free fatty acid/ml/hour) than in more mature preterm infants⁵ (26.8 (13.3) μmol free fatty acid/ml/hour), term infants⁶ (16.0 (6.8) μmol free fatty acid/ml/hour), and adults⁶ (17.5 (6.3) μmol free fatty acid/ml/hour). We also found that the mean activity of postheparin plasma lipoprotein lipase in the very low birth weight and small for gestational age infants was lower than in the infants of appropriate weight. Hence, our results agree with the finding that the elimination of fat in infants less mature than 32 weeks of gestation or infants who are small for gestational age is slower than in infants of appropriate weight.¹³

We measured the activity of postheparin plasma lipase 15 minutes after a heparin bolus of 100 IU/kg whereas the other investigators have measured PHLA 5-10 minutes after a heparin bolus of 10 IU/kg.²⁻⁴ Stahl *et al* have speculated that our large bolus of heparin not only releases the endothelial lipoprotein lipase but also stimulates lipase synthesis within adipose and muscle tissues,⁴ which results in higher lipase activities. In vitro, however, heparin neither stimulates lipoprotein lipase synthesis nor activates the lipase.¹⁹⁻²⁰ Instead heparin releases the functional lipoprotein lipase from the endothelial vascular surface and intracellular pool.²¹ Also, intralipid and very low density lipoprotein particles are capable of releasing functionally active intracellular lipoprotein lipase.²² Whatever the origin of the lipoprotein lipase activity released by 100 IU/kg heparin, in adults it correlates with the elimination of fat emulsion injected intravenously.²³

Poor elimination of the fat infused into the circulation of preterm infants results in triglyceridaemia, the extent of which is in inverse proportion to gestational age.^{4, 18} In preterm infants less mature than 27 weeks of gestation, PHLA is less than 30% of the PHLA found in more mature preterm and term infants.²⁻⁴ This has led to the suggestion that lipoprotein lipase activity increases with gestational age. In our preterm infants postheparin plasma lipoprotein lipase activity was independent of gestational age but correlated positively with birth weight. Gestational age and birth weight are, however, strongly interdependent during the last

trimester of pregnancy. When the effects of birth weight and relative birth weight were removed by statistical means, lipoprotein lipase correlated negatively with gestational age. This means that lipoprotein lipase activity decreases with gestational age, contradicting the earlier suggestions.^{2-4, 18} Thus the negative correlation of lipoprotein lipase with gestational age may provide a partial explanation for our finding that lipoprotein lipase activity was higher in preterm than term infants.

In animals lipoprotein lipase activity increases with postnatal age.²⁴ In preterm infants, however, we found no increase of postheparin lipoprotein lipase activity with age, although an increase of lipoprotein lipase activity has been documented during total parenteral nutrition in term infants.¹³

Postheparin plasma lipoprotein lipase activity correlates with birth weight and relative birth weight, in agreement with the positive correlation between the peak PHLA and body weight.⁴ In adipocytes lipoprotein lipase activity correlates with fat tissue weight.²⁵ Perhaps the poor elimination of the fat infused in preterm infants less mature than 32 weeks' gestation is explained by low birth weight instead of young gestational age. Animal studies on fat deposition indicate that lipoprotein lipase hydrolyses fatty acids and glycerol from chylomicron triacylglycerol; fatty acids are then transported into the adipocytes for re-esterification to cellular triglycerides.²⁶

In our preterm infants the mean (SD) postheparin plasma activity of hepatic lipase (60.0 (26.0) μmol free fatty acid/ml/hour) was as in term infants (54.2 (18.0) μmol free fatty acid/ml/hour)⁶ but about three times higher than in adults (23.1 (11.0) μmol free fatty acid/ml/hour).⁶ There is evidence that hepatic lipase participates in the metabolism of the phospholipids and cholesterol of high density lipoproteins by increasing the flux of free cholesterol into the target tissues.⁸ In vitro, hepatic lipase is, however, also capable of hydrolysing triglycerides and the phospholipids of fat emulsion particles.²⁷ Also, in familial lipoprotein lipase deficiency the intact hepatic lipase hydrolyses triglycerides in very low density lipoproteins.²⁸ High hepatic lipase activity may thus contribute to the hydrolysis of triglycerides in infants. The importance of high hepatic lipase activity, however, in the lipid metabolism of preterm infants cannot be evaluated at the moment because the function of hepatic lipase is not known.

Newborn infants may be incapable of sufficient carnitine synthesis and are therefore dependent on nutritional sources of carnitine.⁹ Our preterm infants were principally fed with breast milk. Their daily carnitine intake was 1.6, 8.2, and 9.6 $\mu\text{mol/kg}$ at the age of 2, 7, and 26 days. Thus the intake at the

age of 7 and 26 days was as in term infants and adults.²⁹ The mean serum concentration of total carnitine in our preterm infants, however, was much lower than in breast fed term infants at the age of 2 (59.3 nmol/ml) or 6 months (62.5 nmol/ml),²⁹ although the serum carnitine concentration in cord blood is usually higher in preterm than term infants.¹⁶

At the age of 7 days in our infants of appropriate weight urinary carnitine excretion and acyl/free carnitine-ratio was as in preterm infants.¹¹ Carnitine excretion decreased with increasing relative birth weight: it was lower in appropriate weight infants than in infants who were small for gestational age. In addition, urinary acyl/free carnitine-ratio was low in the infants who were small for gestational age, which means that most of the carnitine they excreted in urine was free carnitine, as is the case in trauma patients and in renal tubular diseases.³⁰

In conclusion, our study showed that lipoprotein lipase activity in very low birth weight, small for gestational age, and appropriate weight preterm infants was higher than in more mature preterm infants, term infants, and adults. This indicates that the slow elimination of fat from the circulation in preterm infants less mature than 32 weeks' gestation can hardly be explained by low lipoprotein lipase activity. Instead, the low serum carnitine concentrations of preterm infants and the large excretion of carnitine, especially in infants who were small for gestational age, might explain the slow elimination of fat.

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Diagnosis of functional illness presenting with gait disorder

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SUMMARY Nine children presented with disturbances of gait that were not caused by organic disease. They all fulfilled at least four out of eight diagnostic criteria. Diagnosis in all had been delayed while organic causes were excluded. Unnecessary and sometimes potentially harmful procedures were performed or proposed for each child. Identification of such children earlier may avoid morbidity and facilitate management.

Goodyer and Taylor summarised the diagnostic criteria that may aid the clinician in identifying functional disease.¹ These include a history of important events in the child's life, covert family problems, similar symptoms in the past, important information concealed even on direct questioning, a person with similar symptoms in the child's family or peer group, and a discrepancy both between the symptoms and the signs and between the deficits elicited by functional testing and those found on formal clinical examination. Lastly, despite the apparent seriousness of the presentation the signs elicited suggest neither an anatomical site nor a physiological reason for the lesion. The features tend to correspond to the patient's idea of physical illness, and the symptoms may serve an unconscious need.

We report nine cases of functional disease in which gait disturbance was the presenting feature. Eight criteria that aided the diagnosis of hysteria are examined for each case, and their relevance to this group of patients discussed. All children were seen in the rheumatology clinic, except for one who was referred to the neurology clinic.

Case reports

CASE 1

A girl was referred with a three week history of being unable to walk associated with pains in the right knee and ankle that were severe enough to prevent her attending school. She had had intermittent fever for six months that was resistant to aspirin; general malaise and sore throat for four weeks, and aches in her neck, left arm, and left chest for three weeks.

She entered the room hopping on her left foot, and was extremely apprehensive and difficult to examine. There were, however, no signs of inflammation in the right leg, or any other abnormal findings. She was admitted to hospital for assessment during which time she was not feverish, and her movements were less restricted when she thought she was unobserved. C-reactive protein concentration, erythrocyte sedimentation rate, x ray pictures of the ankles, knees, and hips, and bone scan of the ankles were all normal.

A functional illness was suspected, and further investigations were postponed. Assessment by the physiotherapist confirmed the discrepancy between her claimed abilities and actual function. Enquiry elicited that she had recently been bullied at school, and that her symptoms started after this. She was discharged home having physiotherapy to aid mobilisation, and had recovered completely after two weeks. She subsequently changed schools.

CASE 2

A boy was referred to the orthopaedic clinic with a throbbing pain in his right hip after a fall on wet leaves when playing rugby football. Due to his father's change of job the family had recently moved to the area from a distant part of England where he had twice been admitted with an 'irritable hip' that had settled after traction.

There were no abnormal physical signs, and his erythrocyte sedimentation rate and x ray picture of the hip were normal, so rest was advised. During the next weeks he deteriorated despite traction, physiotherapy, rest, gentle mobilisation on crutches, and hydrotherapy. A bone scan suggested Perthes' disease but a repeat bone scan and radiographs

appeared normal. Operation was considered, but he was referred for the rheumatologist's opinion first.

He had by now had symptoms for nine months, and had needed crutches for 12 weeks. He was hopping for four to five hours a day to remain mobile, and sometimes used a wheelchair. There was, however, no evidence of muscle wasting, and rotation of the hip was normal. He had a full range of knee movements. He could kiss both knees thus showing a degree of mobility that he denied when tested formally. Further enquiries showed that he had been under considerable stress before the illness. After the recent move he had disliked his new school and preferred the tuition at home that had been arranged for him while his symptoms persisted.

He was referred to a child psychiatrist who diagnosed a functional illness that had started after he had had a genuine irritable hip. He was mobilised with physiotherapy, and improved in the first four weeks. The family then stopped attending psychotherapy sessions. Three months later he suffered a relapse. The family were contemplating a move back to the area of England where he had been happiest, and they failed to keep further appointments.

CASE 3

A girl was referred by her general practitioner. She had had a sore throat that had been followed by weakness of her legs that had confined her to a wheelchair for three weeks. She had recently started at secondary school where she was said to be progressing well.

She was a prepubertal girl who was anxious when examined, but seemed otherwise remarkably untroubled by her illness. Her lower limbs were not wasted but she would not move them. She could stand hesitantly, but was unsteady if she tried to walk. Two weeks later, however, she seemed to have developed clonus in her right ankle and bilateral increased knee jerks though the plantar reflexes were downgoing. She was admitted to hospital for investigation to exclude a spinal lesion. Spinal x ray pictures, examination of cerebrospinal fluid, myelogram, erythrocyte sedimentation rate, and virological titres were all normal. A provisional diagnosis of transverse myelitis was made, and she was treated with physiotherapy.

After two weeks her walking had deteriorated further, so she was admitted to hospital for reassessment. The nursing staff noticed that her symptoms fluctuated in severity, being worst while her over-protective mother or a member of the medical staff was nearby. Assessment by the physiotherapist confirmed that there were no abnormal signs, and

muscle function during hydrotherapy was better than on formal testing. A psychiatrist discovered that the girl had twice had similar symptoms following minor illnesses several years before, and that she had recently been teased at school; both these facts had been concealed until then. He diagnosed a functional illness and told the girl and her mother that the symptoms would resolve rapidly. She began walking the next day, and two weeks later she returned to school.

CASE 4

A 14 year old girl gave a history of 12 months of intermittent pain on the medial aspect of the right foot that sometimes woke her at night. She had missed at least four weeks of school, the family's annual holiday in Spain had been cancelled, and she had been confined to the house during the summer holidays. Three years previously she had complained of pains in both knees and the surrounding muscles but despite investigations no diagnosis had been made. The family had not attended follow up appointments.

Examination showed mild tenderness over the extensor digitorum brevis but no other signs, and x ray pictures of the knee were normal. Remedial foot and ankle exercises produced no improvement, and two months later she was unable to bear weight on the right foot and needed crutches. There was, however, no evidence of arthritis, and she had a full range of passive movements at the ankle. Her degree of disability did not seem commensurate with the signs, so she was admitted to hospital for assessment.

Serum C-reactive protein concentration and erythrocyte sedimentation rate were normal, and a technetium 99 bone scan showed minimal asymmetry of the uptake of isotope in both ankles. Observation on the ward, meanwhile, confirmed that she was less disabled than her account had suggested. She was able to move on her bed without pain or stiffness.

A functional illness was suspected, further investigations were postponed, and a psychiatrist confirmed the diagnosis. She made a good recovery after seven weeks in a psychiatric ward. The precipitating and perpetuating factors never became clear, but academic pressure, bullying at school, and sibling rivalry for her father were all possibilities.

CASE 5

A girl was referred from the orthopaedic department for assessment with a 12 month history of pain in the left heel that had been precipitated by a fall during a crucial game of rounders and exacerbated by subsequent falls at school and in the local

shopping area. She had been unsuccessfully treated with a below knee plaster and walking heel on two occasions six months apart, and physiotherapy was also unsuccessful. Local injection of hydrocortisone had been considered, but examination and investigation failed to confirm inflammation.

Her illness had forced her to give up dancing, which was her main recreation, and she was unable to take part in games at school. She had, however, managed to attend lessons on crutches for the previous six weeks. She had epilepsy that was controlled with carbamazepine. Her mother had been off work for several months three years previously with a slipped disc.

On examination there was slight puffiness round both achilles tendons but she had a good range of active and passive movements with no crepitus. She had full and painless passive movements of all other joints. There appeared to be a gross discrepancy between symptoms and signs, and the possibility that she had a functional illness was considered. The mother agreed with this assessment, volunteering the information that the symptoms seemed to be used to avoid stress.

After discussion with the parents, rehabilitation with intensive physiotherapy was started. She made a good recovery in five weeks, was encouraged to start dancing again, and to take part in all sports. She was well on review four months later, though she occasionally still missed sport at school.

CASE 6

A girl was referred from the orthopaedic department with a four month history of pain and stiffness in the left knee, which she could not extend. She needed crutches. Physiotherapy had apparently exacerbated the symptoms. Arthroscopy of the knee had been normal, after which her symptoms had progressed to the extent that she was unable to play games or join in with other children at school playtime.

She had had pains in the left elbow and knee in the previous year that were not diagnosed, and which resolved spontaneously. She was an only child whose parents had divorced six years previously. She saw her father every Sunday. Her mother had suffered from chronic osteomyelitis of the tibia since the age of 9 and had recently been referred to the local pain clinic.

She had full active movements of all joints except the left knee, which she was reluctant to move. Passive flexion of the left knee, however, was possible up to 90° without pain despite considerable quadriceps spasm. In contrast to the history, passive extension of the knee showed a full range of painless movement. Because of the discrepant

symptoms and signs, a functional illness was suspected. The physiotherapist said that the symptoms were inconsistent and fluctuant, and a psychiatrist confirmed the diagnosis.

The child's symptoms were thought to be an emulation of the mother's disability due to chronic osteomyelitis, and the friction between the divorced parents seemed to be a major factor. Within two weeks, although she appeared no better to her mother, she abandoned the crutches at school and returned to full activity. Her symptoms had resolved six months later.

CASE 7

A girl was referred by her general practitioner with a five month history of pains in the arms, stiff neck, and numbness of the fingers, followed by pains in the right knee. She had not been taking part in sports for the previous month.

She had previously been seen in the orthopaedic outpatient clinic and a collar and a splint were prescribed, with little benefit. Haematological investigations were normal. Her mother had cervical and lumbar spondylosis, and her father had recently had a subarachnoid haemorrhage.

The discrepancy between her symptoms and lack of signs suggested a psychological basis for her symptoms. Assessment by the physiotherapist confirmed this, and a programme of rehabilitation was started. Two months later she was back to full activity with only occasional pains in her knee. She mentioned that her father too was better.

CASE 8

A boy was referred for a second opinion by his general practitioner. After a fall he had complained of pain in the left hip for five months, and had been off school for three months. The previous year he had been admitted to hospital on four occasions with an irritable left hip, and had had an exploratory arthrotomy on the last occasion.

He had been born by caesarean section, and had been separated from his mother for some weeks after birth because she had been on traction for pains in her left leg. He was an only child in his first year at secondary school.

He was a tearful, obese boy who limped dramatically when asked to go to the examination couch, but apart from some antagonistic muscle action in his left hip there was no evidence of inflammation or restriction of active movement. After admission to hospital he limped only intermittently, but particularly when under observation. Haematological investigations were normal, as were thyroid function tests, serum immunoglobulin concentrations, Tine test, and culture of the urine. An ultrasound scan

showed a possible small effusion in the left hip joint. A bone scan was normal.

Assessment by the physiotherapist confirmed the discrepancy between formal signs and functional testing, and a programme of rehabilitation was started. Psychiatric consultation elicited the fact that his own anxiety about his health was reinforced by overprotective parents. His symptoms had not improved seven months later. The family defaulted from follow up, but attended the orthopaedic department again where the symptoms were treated as organic; synovial biopsy was repeated and the specimen was normal.

CASE 9

A 9 year old girl was referred by her general practitioner with a three month history of pain in the

right knee followed by pains in both lower legs and difficulty walking after an injury to the right knee. Her mother was divorced but had a regular boy friend. Considerable social problems were suspected.

She was obese, hobbled and appeared to have painful feet. She had, however, good active and passive movements of all joints. There was a little puffiness around the right ankle but no consistent local tenderness.

She was admitted to hospital for investigation. Haematological investigations were normal, as were erythrocyte sedimentation rate, C-reactive protein concentration, latex test for rheumatoid arthritis, immunoglobulin concentrations, thyroid function tests and culture of the urine. Antinuclear factor activity was absent. Mild osteoporosis of the ankles

Table 1 *Features of the nine patients with functional gait disorders*

	1	2	3	4	Case No				
					5	6	7	8	9
Sex	F	M	F	F	F	F	F	M	F
Age at presentation (years, months)	11,0	11,4	12,5	14,10	12,10	9,9	10,8	12,11	9,7
Length of history (months)	6	9	1	14	12	4	5	5	3
Duration of gait disorder at presentation (weeks)	3	12	3	4	6	16	4	14	12
Time from presentation to diagnosis (days)	8	1	56	42	1	1	1	1	22
Time from diagnosis to recovery (weeks)	2	4	2	8	5	14	4	32	21
Total time unwell (months)	6½	10	1½	17½	13	7½	6	13	9
Length of follow up from presentation (months)	3	3	4	3	4	6	13	28	5
Outcome	Good	Relapse, did not attend	Good	Good	Good	Good at school, poor at home	Good, knee pains	Did not attend, attends orthopaedic clinic	Did not attend

Table 2 *Features aiding diagnosis in nine patients with functional gait disorders*

	1	2	3	4	5	Case No				9	Total No
						6	7	8			
Important events in the child's life	-	+	-	-	-	+	+	+	+	+	5
Presence of a model for their symptoms	-	-	-	-	+	+	+	+	-	-	4
Past history of similar symptoms	-	+	+	+	-	+	-	+	-	-	5
Concealed history	+	+	+	+	-	-	-	-	+	+	5
Covert family problems	-	+	+	+	-	+	-	+	+	+	6
Discrepant symptoms and signs	+	+	+	+	+	+	+	+	+	+	9
Discrepant signs and function	+	+	+	+	+	+	+	+	+	+	9
Signs did not localise lesion	+	+	+	+	+	+	+	+	+	+	9
Total (maximum 8)	4	7	6	6	4	7	5	7	6		

- =No, + =Yes.

and feet was apparent on x-ray pictures, with possible cortical bony loss in some areas. In view of this, despite the suspicion of functional disease, bone marrow was aspirated, examination of which was normal.

Her symptoms were thought to be largely psychological with some secondary sympathetic dystrophy. During assessment in hospital she said that her mother's boy friend was violent, and she had seen her mother being attacked and threatened on many occasions.

She was treated with psychotherapy and physiotherapy in hospital, and limped when her mother visited. The mother refused psychological and social help, and removed her daughter after six weeks. The girl hobbled out of the ward where the night before she had danced at a leaving party held for her by the nursing staff.

Table 1 shows the features in the nine children, and table 2 shows the diagnostic features in each case according to the criteria of Goodyer and Taylor.¹

Discussion

Failure to walk usually implies severe organic disease and may therefore warrant complex and potentially harmful investigations. Although none of these nine children came to actual harm, cases 1, 4, 5, and 6 were admitted for a number of investigations, case 2 nearly had an operation, and cases 3, 5, 6, and 8 had invasive procedures performed before functional causes were seriously considered. In retrospect most of the tests were unnecessary, although at the time it was thought important to exclude organic disease. Indeed, in case 9 examination of the bone marrow was performed after the diagnosis of functional illness had been considered because an x-ray picture had suggested infiltration of the marrow.

Up to 30% of adults thought to have functional illness subsequently turn out to have organic disease,² and although this is not the case in this series it must be borne in mind. It is not until organic disease has been ruled out that most families are ready to consider the possibility of functional disease; premature discussion about this can antagonise parents. On the other hand, multiple tests to exclude the many possible diagnoses tend to reinforce parental belief that there is an organic basis for the symptoms.

Children with pains in the joints and limbs often have additional psychological problems. In a study of rheumatological outpatients, 9% were thought to have functional illnesses that entirely accounted for their symptoms.³ Children who present with

inability to walk may, however, be referred to other clinics. The cases reported here presented to rheumatological, orthopaedic, and neurological clinics: all doctors who treat children thus need to be aware of this presentation of functional illness.

It is important to look positively for functional illness to avoid potentially damaging investigations or treatment. The examination of the patient is the most useful pointer towards diagnosis. All our cases fulfilled the examination criteria cited by Goodyer and Taylor. All fulfilled at least four of the total of eight criteria, though fewer historical criteria were met.

Management is often difficult. Three points were made by Dubowitz and Hersov who reported five children with functional disorders of motor function.⁴ Firstly, investigations should be kept to a minimum, and must be stopped when the diagnosis is suspected. Secondly, they suggested that paramedical staff have an important part to play in management. This was so in our series. Experienced nursing staff observed discrepancies in the child's abilities in the ward in cases 1, 3, 8, and 9. Physiotherapists detected inconsistencies in the patient's claimed power deficits in cases 3, 6, 7, and 8. After assessment a planned programme of physical activities should be started by an experienced physiotherapist in liaison with the clinician. This allows the child to regain full function while saving face and dignity.

Thirdly, psychiatric assessment should be requested to confirm the diagnosis, and find out why the child is behaving in such a way. Supportive psychotherapy for the child and the family during the period of follow up may assist rehabilitation. Six of our nine cases were seen by psychiatrists who uncovered more diagnostic information, and confirmed the diagnosis of functional illness in all.⁵ Not all families, however, agree to psychiatric consultation and follow up.

Identification of the unconscious need that is causing the symptoms is not always possible. Only two of our children had strong dislike of school as part of the reason for illness. Others were able to control their families at times when they felt in particular need of security. In most, several factors were undoubtedly present. Perhaps these children were all telling their families that they 'could not stand on their own two feet'.

There is a temptation to confront the child with suspicions about the functional nature of the diagnosis in an effort to terminate the episode. This should be resisted; it usually does not produce the desired effect, and there is a risk of precipitating deterioration in the presenting symptoms and, rarely, the appearance of new ones.

The outcome in these cases ranges from rapid and total recovery to continuing disability. Those with persisting symptoms often defaulted from follow up or attended other clinics where the problem was managed as organic, so conferring respectability on the illness in the eyes of the parents and the child.

In the present series mother and child sometimes colluded in concealing crucial details, or frustrated attempts at treatment. In the latter circumstance it is important that the way is left open for the re-establishment of a treatment programme in the future, and to this end all effort should be made to maintain contact with the child and the family.

There were four children in whom the eventual outcome was poor; three had a score of seven and the fourth a score of six. It is possible that a high score at presentation would correlate with a poor outcome, but there are not enough children in this series to allow firm conclusions. It should be noted that the nature of some of the items in the score—for example, a concealed history—makes their identification at presentation difficult and the score incomplete.

Ideally, medical follow up of patients needs to be considerably longer than that for most of these cases, even if physical recovery appears complete. Psychosocial pressures may precipitate further

symptoms related to stress that could be swiftly identified and treated, so avoiding morbidity. Five of these nine cases had had previous similar symptoms

In conclusion, the appreciation of the functional nature of an illness in children presenting with disorders of gait may be aided if the eight criteria summarised here are used in the assessment of the child, those concerning the examination of the child being the most important.

We thank Dr JR Roberts for permission to report case 3

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Two mutations of dihydropteridine reductase deficiency

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SUMMARY Two patients with dihydropteridine reductase (DHPR) deficiency, in one case due to the absence of any enzyme protein (DHPR⁻ cross reactive material (CRM)⁻) and in the other case due to the production of a mutant type devoid of catalytic activity (DHPR⁻ CRM⁺) were examined. This latter form of malignant phenylketonuria, whose relative frequency seems to be higher in the Italian population, possibly has a worse prognosis. The earlier onset and the greater severity of clinical symptoms are associated with a more pronounced hydroxylation defect, as shown by higher degree of neonatal hyperphenylalaninaemia, unresponsiveness to an oral tetrahydrobiopterin load, lower concentrations of neurotransmitter metabolites, and reduced tyrosine production after an oral phenylalanine load.

The first observation that concerns the lack of response of phenylketonuric children to dietary treatment is that of Mary Efron in 1965 reported by McKusick.¹ Dr Efron pointed out that phenylketonuria (PKU) seldom affects people of southern Italian origin, but when it does, it is unresponsive to diet and causes death in the first years of life. The observation may have been the result of some type of tetrahydrobiopterin (BH₄) deficiency, which was not recognised at that time, as a possible cause of primary hyperphenylalaninaemia. This hypothesis is supported by the recent finding that among people of southern Italian origin the frequency of BH₄ deficiency seems higher than in other populations, mainly due to the higher prevalence, and clustering in Sicily, of dihydropteridine reductase (DHPR) deficiency.² As this form of atypical PKU is known to be heterogeneous with respect to the molecular defect³ and the response of an oral BH₄ load,⁴ two patients deficient in DHPR, originating from the south of Italy and with different clinical presentations, were evaluated in an attempt to determine a correlation with their enzyme state and BH₄ responsiveness.

Case reports

A girl (case 1), born on 20 February 1983, was the

second child of second cousin parents originally from Calabria, a region of southern Italy. She had 7 mg% plasma phenylalanine at 4 days of age on Guthrie mass screening, and had confirmed diagnosis of hyperphenylalaninaemia (1268 µmol/l) at the age of 20 days when a phenylalanine restricted diet was started. Physical and neurological development was judged to be normal up to the age of 7 months, although head circumference seemed to be reduced from the sixth month. Her phenylalanine tolerance, unlike that in PKU, was stable at the high value of about 50 mg/kg/day. Over the next few months it was evident that she was slow in reaching developmental milestones and there was subsequent regression with progression of the typical neurological picture of BH₄ deficiency. An electroencephalogram gave repeatedly normal results, and no episodes of hyperthermia occurred. The diagnosis of DHPR deficiency was made at the age of 10 months and treatment with levodopa, 5-hydroxytryptophan, and carbidopa was added to the phenylalanine restricted diet. After several adjustments,⁵ the clinical response to the treatment was good. The girl is now attending a kindergarten, has no gross motor or speech disabilities, and her intelligence quotient was 95 at the age of 3 years and 9 months.

A boy (case 2), born on 4 April 1983, was the third child of first cousin parents who originated

from Sicily. A neonatal Guthrie test was not done and he was on a free diet until the age of 10 months when the hyperphenylalaninaemia was ascertained (1320 $\mu\text{mol/l}$). Difficulty in feeding, extreme truncal hypotonia, and eye deviation had appeared in the first two months of life, and by the fifth month psychomotor deterioration, microcephaly (head circumference below the third centile), repeated daily myoclonic convulsions and hypersarrhythmic activity shown on electroencephalography were present. A phenylalanine restricted diet was started at 10 months, and neurotransmitter treatment was added at 13 months after the diagnosis of DHPR deficiency. Despite the severity of the clinical picture and the delay in beginning treatment, the patient slowly improved. Convulsions stopped within six months with electroencephalography giving normal results. Motor disabilities and behavioural abnormalities diminished and head circumference increased (it is now over the 10th centile). At 2 years 6 months of age the patient started walking and speaking some simple words; his intelligence quotient, however, was only 45 at the age of 3 years and 5 months.

Methods and results

The activity of DHPR was measured by assay of dried blood spots⁶ and on cultured fibroblasts.⁷ Both methods showed no activity in the patient's cells. All four parents exhibited intermediate values (table 1).

Immunoprecipitation of DHPR was carried out after labelling of fibroblasts with ³⁵S methionine.^{8,9} Immunoprecipitates were then separated by sodium dodecyl sulphate polyacrylamide electrophoresis according to Laemmli¹⁰ and detected by fluorography. The method was sensitive enough to detect 5% of normal enzyme concentrations. Cross reactive

material (CRM) was present at near normal concentrations in the boy (case 2) and was absent in the girl (case 1); this has already been reported by us.⁹

Serum folate measurements were performed by means of a commercial radioassay kit (Ciba Corning MAGIC Vitamin B₁₂/Folate NB) at diagnosis and after 10 days of oral administration of folic acid at 15 mg/day (table 1). Only the girl was found deficient in folate, but both patients failed to show any metabolic or clinical improvement with this treatment.

An oral BH₄ loading test was given to both patients.¹¹ As the boy showed no reduction in plasma phenylalanine concentrations he was given 2 mg/kg BH₄ intravenously, to which he responded partially (table 2).

Urine and cerebrospinal fluid (CSF) pterins, CSF neurotransmitter metabolites, homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA) were measured by high performance liquid chromatography with electrochemical detection at high and low plasma concentrations of phenylalanine (table 3).¹² The urinary and CSF pterin patterns were similar in the two patients, in both of whom the pterin pattern reverted towards normal under dietary treatment. At diagnosis the boy showed

Table 2 Plasma phenylalanine response to loading with tetrahydrobiopterin (BH₄) in the two patients

Case No and route of administration of BH ₄	Dose of BH ₄ (mg/kg)	Plasma phenylalanine concentration ($\mu\text{mol/l}$)		
		0	4 hours	8 hours
Case 1 oral	7.5	478	208	110
Case 2. oral	7.5	1386	1380	1344
intravenous	2.0	960	934	764

Table 1 Dihydropteridine reductase (DHPR) activity in dried blood spots and in cultured fibroblasts of the two families, and serum folate values in the patients before and after folic acid treatment

	DHPR activity		Serum folate (ng/ml)	
	Erythrocytes	Fibroblasts	Day 0	Day 10
Case 1	None detected	None detected†	2.7	20
Father	1.14	Not determined		
Mother	1.82	Not determined		
Case 2	None detected	None detected	20	43
Father	1.37	Not determined		
Mother	0.92	Not determined		
Controls	3.34 (0.88)* (n=20)	49.6 (2.8)† (n=11)	3-17	

*Value is mean (SD) (nmol cytochrome C reduced/minute/5 mm diameter, filter paper disc)

†Value is mean (SD) (nmol NADH oxidised/minute/mg protein)

‡1% of normal activity could be confidently assayed

Table 3 Pattern of *pterins* in urine and cerebrospinal fluid; concentrations of homovanillic acid (HVA) and 5-hydroxytryptole acetic acid (5-HIAA) recorded in the two patients at basal conditions and during phenylalanine restricted diet with substitutive neurotransmitter treatment

Case No	Age (months)	Treatment	Plasma phenylalanine concentrations (mg%)	Urine				Cerebrospinal fluid			
				Biopterin	Neopterin	%B*	BNCR†	Biopterin	Neopterin	HVA	5-HIAA
				(mmol/mol creatinine)				(nmol/l)			
Case 1	14-24	‡ Restricted diet, levodopa, 5-hydroxytryptophan, carbidopa	6	6.51	1.02	86	563	57.3	11.4	81.0	23.0
			3	4.03	2.80	59	237	50.9	23.7	681	334
Case 2	13-23	‡ Restricted diet, levodopa, 5-hydroxytryptophan, carbidopa	24	13.8	2.86	83	1143	63.1	10.5	50.8	6.9
			3	1.95	1.29	60	117	38.6	15.5	474	173
Healthy controls				1.10	0.47	44	33	10	9	250	110
				4.00	3.00	77	139	34	20	880	360

*%B = $100 \times (\text{biopterin} + \text{neopterin}) / \text{bipterin}$.†BNCR (bipterin:neopterin creatinine ratio) = $\text{bipterin} / (\text{bipterin} + \text{neopterin}) \times \text{bipterin} \times 10^5$.

‡In both cases the treatment was discontinued for more than a week: in case 1 because the drugs were not available and because of the high phenylalanine tolerance, in case 2 the parents were initially not fully convinced of the benefit of this treatment.

lower HVA and 5-HIAA concentrations in the CSF than the girl, but he also had higher phenylalanine concentrations. Correction was achieved in both patients with similar doses of hydroxylated neurotransmitter precursors.

An oral load of phenylalanine (0.6 mmol/kg) was given,¹³ and amino acids were measured chromatographically with the Kontron Chromakon 500 automatic analyser. The impairment of hydroxylating activity was possibly more pronounced in the boy, as

indicated by a somewhat slower fall in plasma concentrations of phenylalanine and lesser rise in tyrosine (figure).

Discussion

Clinical variation in patients with inborn errors of metabolism is common due to quantitative as well as qualitative differences in underlying mutations and additional factors. Three different enzyme defects

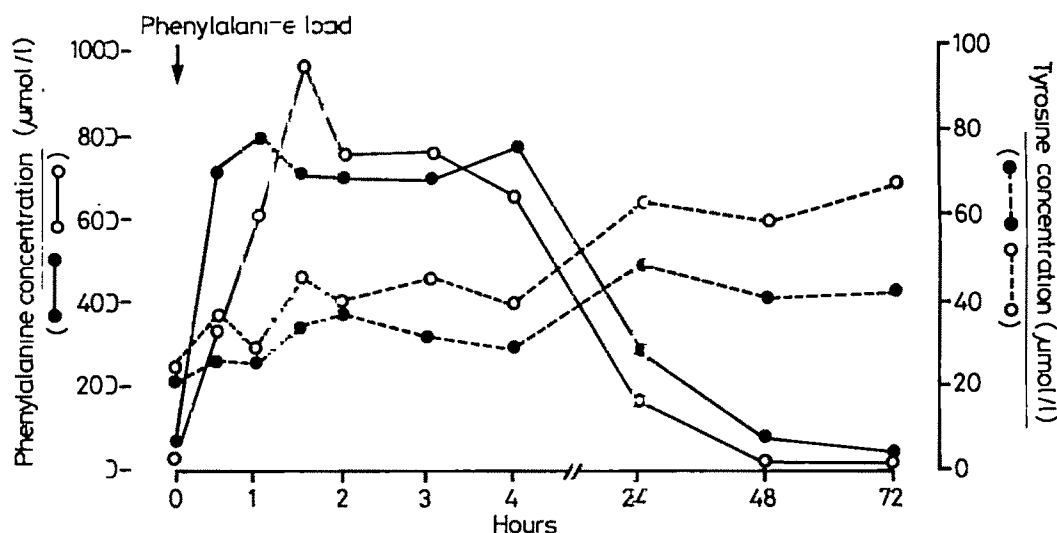


Figure Plasma phenylalanine (—) and tyrosine (---) responses to an oral phenylalanine load in the girl (○) who did respond to the load with tetrahydrobiopterin (BH_4) and the boy (●) who did not respond.

cause BH₄ deficiency, guanosine triphosphate cyclohydrolase I (GTP-CH I) and 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency causing impaired synthesis and DHPR deficiency causing impaired recycling of the cofactor.⁴ Further heterogeneity has been described within these defects.¹⁴ The use of a BH₄ oral load as a diagnostic tool has shown that a minority of patients deficient in DHPR fail to lower their plasma phenylalanine after loading,⁴ and in addition it has been shown that some patients have no mutant protein (DHPR⁻ CRM⁻) in their cells, whereas others have (DHPR⁻ CRM⁺).^{3, 15} It has been reported that CRM⁻ cases are BH₄ responders and CRM⁺ are non-responders and that the latter have a worse prognosis.⁹

The present study strengthens the hypothesis that the presence of the mutant DHPR is worse clinically: shown by the earlier onset of symptoms and the relatively poor clinical response to neurotransmitter treatment in the patient with CRM⁺, although the delay in starting a phenylalanine restricted diet could also have contributed.

Contrary to the opinion that the unresponsiveness to exogenous BH₄ could be due to the total deficiency of DHPR catalytic activity,¹⁶ this was present in both our patients and only the child who was CRM⁺ gave a negative response after oral loading. Unresponsiveness to exogenous BH₄ could be due to the binding of cofactor to the mutant enzyme, making BH₄ unavailable for hydroxylation. If so, a decrease of plasma phenylalanine might be achieved by loading these patients with doses of BH₄ large enough to exceed the CRM⁺ binding capacity; the CRM⁺ patient described here did respond to intravenous BH₄, and together with another non-responding patient also responded to higher oral doses.¹⁷ Alternative hypotheses might be the production of a reactive pterin, which inactivates hydroxylases, or the inhibition of the hydroxylases by the mutant enzyme. In any of these cases, the endogenous biosynthetic BH₄ would be less available in CRM⁺ patients, leading to a worse outcome. The CRM⁺ patient described here may have had a more pronounced hydroxylation defect than the child who was CRM⁻ in view of the lower basal concentrations of HVA and 5-HIAA, and the reduced tyrosine production after oral phenylalanine load. Furthermore neonatal hyperphenylalaninaemia has been reported to be higher in patients who were CRM⁺ than in patients who were CRM⁻.⁹

Within the DHPR deficiency the relative frequency of non-responding and responding cases to the oral load of BH₄ has been reported in worldwide surveys as 1:3–1:4,^{4, 14} although this may not be true for the Italian population, as two out of four

patients, both originally from Sicily, did not respond to the load.² A continuum of conditions is to be expected, depending on differences in the mutations. Cases with residual reductase activity¹⁸ or partial CRM⁺⁹ are known to have a milder course.

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Joint mobility and motor development

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SUMMARY The association of joint hypermobility and motor development was sequentially investigated in 715 infants from the ages of 8 to 14 months. Seven joints were evaluated for mobility, and each infant underwent a physical and neurological examination. Parents were given a Denver Developmental Parents' Questionnaire. All subjects with a general developmental delay, systemic illness or syndrome were excluded. The infants were classified as having normal or delayed motor development with normal or delayed joint mobility. They were re-examined six months later. Multivariate statistical techniques were used for categorical analysis, and three joints were found to be significantly associated with motor delay at the first examination—hip abduction, elbow hyperextension, and foot dorsiflexion. Of the 715 infants, 126 had joint hypermobility and of these 38 (30.2%) had motor delay. Sixty-four of 589 (10.9%) with normal joints had delayed motor development. Six months later 23 out of 35 of the group with joint hypermobility and 42 out of 53 of the group with normal joints had normal motor function.

Joint hypermobility is associated with an increased incidence of motor delay in infancy. Over the ensuing six months most of the subjects will catch up. These findings, indicating a favourable prognosis, have implications regarding clinical assessment and parental counselling.

Paediatricians frequently encounter infants presenting with delayed gross motor development. The evaluation of such cases entails comprehensive paediatric and neurodevelopmental examination, and when cerebral palsy, mental retardation, and other neuromuscular aetiologies have been excluded, a group of slow motor developers of unknown aetiology and prognosis remains. The rather dramatic presentation of an infant who does not attain sitting, crawling, or walking at the same time as his peers often engenders anxiety in the parents. It has been our experience that a number of these infants have hypermobile joints and that they ultimately seem to catch up in motor development.

Previous reports suggest that hypermobile joints can be the result of either increased laxity of the ligaments and joint capsule or muscle hypotonia.² Owing to the inherent difficulties of clinically quantifying degrees of muscle hypotonia we studied the problem by assessing joint mobility and did not attempt to differentiate between the two possible causes. Hypotonia associated with slow motor development has been described,^{2,3} and one study has investigated the association of joint hypermobility

and motor development.⁴ No prospective, controlled blind studies, however, have been performed.

The two main purposes of this study were as follows: (a) To investigate whether hypermobile joints were in fact associated with an increased incidence of motor delay, and, if so, whether specific joints were more often affected. (b) In the event of a positive association, to study these infants prospectively in order to elucidate their subsequent motor development and joint mobility as compared with controls.

Patients and methods

Altogether 729 infants from the ages of 8 to 14 months were recruited from 10 well baby clinics and seven day care centres in the Haifa area. Staff at the well baby clinics had previously screened the infants and infants with the following conditions were excluded from the cohort: those with acute or chronic illnesses; those who had recently been in hospital; those suffering from diagnosed neurodevelopmental delay or metabolic disorders; those who had had low birth weight including preterm infants; and those having defined syndromes. An additional

12 infants were excluded by the examining paediatrician: three because of cerebral palsy, six because of general developmental delay, two because of significant cardiac abnormality associated with congestive cardiac failure, and one because of thalassaemia major. The original study sample comprised 717 subjects of whom 365 were boys and 352 girls. This study population presented a cross section of the ethnic and socioeconomic characteristics of the Haifa community.

The study consisted of two stages

Stage I. (1) Information concerning the developmental state of each infant was obtained from the records of the well baby clinic where the results of periodic standard assessments by the nurses using the Stygar Sequence to ascertain the infant's developmental state were rated.⁵ (2) The Denver Developmental Parents' Questionnaire was completed by the parents.⁶ This questionnaire is based on the Denver Development Screening Test (DDST), which unlike the above procedure has been standardised for the Israeli population and was used to determine the present motor developmental state of the child.⁷ It was completed before the joint mobility assessment. For the purposes of this study motor delay was defined as a failure to attain the motor skills achieved by 75% of the Israeli population of the same age.⁷ (3) A paediatrician performed a complete physical and neurological examination, with particular emphasis on the assessment of muscle strength and the presence of normal tendon reflexes. Clinical evidence of connective tissue disorders was also sought. (4) The mobility of seven joints was assessed, five of which were those investigated in other studies (table 1).¹ Hip abduction and shoulder adduction (scarf sign) were added. The paediatrician performing the joint assessment was unaware of the motor developmental state of the infant as reported by the parents and staff of the well baby clinic. (5) Information on demographic data, family history of joint hypermobility, rheumatic diseases, and motor development was obtained

by a questionnaire designed for the purpose of this study. The information was gathered from the parents who were unaware of the joint assessment findings in their offspring.

Interobserver reliability for the joint mobility assessment between the study paediatrician and another paediatrician and reproducibility were established before the initiation of the study. Thirty infants of the same age range as the study population were examined, with a resulting reliability of 90% and reproducibility of 96%. This procedure was repeated during the study on a random sample of 40 infants from the total cohort, and resulted in a reliability of 0.86.

Stage II. Six months later a random representative sample of the cohort was re-examined for joint mobility, and motor achievement was assessed by the DDST.⁷

Statistical analysis. As all joint mobility variables are categorical (most of them dichotomous and one trichotomous), a classical linear discriminant analysis could not be applied. A regression model was therefore used in which the dependent variable was the log odds ratio on the gross motor development variable. The independent variables were the joints included in the assessment, which were modelled as factors.⁸ The statistical package SAS (*SAS Users guide statistics 1982*) was used for computer analysis purposes. The FUNCAT procedure was utilised to model the functions of categorical variables.

Results

Out of the 715 subjects on which complete data was available 525 (73.4%) had normal joints and normal motor development, and 102 (14.3%) with and without hypermobility presented gross motor delay. Eighty eight infants with hypermobile joints had normal gross motor development. To explain the delay various combinations of main effects and interaction were tried from the seven joint mobility variables. In the final model each of the included effects were highly significant. The three joints that best correlated with gross motor developmental delay at stage I were (a) foot dorsiflexion ($\chi^2=13.38$, $p=0.003$); (b) hip abduction ($\chi^2=0.53$, $p=0.002$); (c) elbow extension ($\chi^2=11.25$, $p=0.008$). If all of the three joints were hypermobile the odds of developmental motor delay were 10.11 (that is, 10 times more than the odds from motor delay in the total cohort). If none of the three joints were affected the odds were 0.43 (compared with the total cohort). The relative odds of developmental motor delay were therefore 23 (10.11/0.43).

Table 1 *Assessment of joint laxity*

- 1 Thumb—passive apposition to the flexor aspect of the forearm
- 2 Fingers—passive hyperextension so that they lie parallel with the extensor aspect of the forearm
- 3 Elbow—passive hyperextension to 10° or more
- 4 Knee—passive hyperextension to 10° or more
- 5 Ankle—passive dorsiflexion of foot score (1) for proximal contact and score (2) for complete contact with tibial volar aspect
- 6 Shoulder—passive adduction with elbow crossing chest midline (scarf sign)
- 7 Hip—passive abduction to 180°

One hundred and twenty six subjects showed hypermobility in one or more of these three joints in various combinations. Of these 38 (30.2%) presented gross motor delay as opposed to 64 (10.9%) if none of the three joints were hypermobile (table 2).

Six months later (stage I) a stratified random sample of the cohort was re-examined. Four diagnostic categories (see table 3) were selected as follows: (a) gross motor delay and hypermobility—35 infants (92% of the original group); (b) gross motor delay and normal joints—53 (33% of the original group); (c) normal motor development and normal joints—90 randomly selected (every fifth infant from each clinic) from the 525 subjects who comprised the original group; (d) normal motor development and hypermobile joints—35 randomly selected (every third infant from each clinic) out of the 88 who comprised the original group. Four subjects and two subjects from groups (c) and (d) respectively were excluded from the analysis because of missing data.

Out of the 58 infants with joint hypermobility (comprising both normal and delayed motor development), 44 (75.9%) lost their hypermobility. Out of the 35 who had hypermobility and delayed development, 24 (68.6%) infants lost their hypermobility and 20 (83.3%) of these caught up in motor development. Out of all the 11 whose joints remained hypermobile only six (54.5%) caught up.

(This difference did not reach a significant level but may indicate a trend.)

Over the six month interval between stage I and II the prevalence of gross motor delay in the groups with hypermobile and normal joints remained constant (tables 2 and 3). Factors such as sex, ethnic origin, socioeconomic status, joint hypermobility, or rheumatic diseases in other family members were not found to be significantly associated with the hypermobility in the cohort subjects. Two significant factors associated with joint hypermobility were bottom shuffling and young age (table 4).

Although the reliability of parental recollections

Table 4 The association of other factors with hypermobility and their significance

Factor	χ^2	p Value
Age	26.5	0.0002
Sex	0.004	NS
Ethnic origin	1.85	NS
Socioeconomic status	6.69	NS
Bottom shuffling	6.98	0.0082
Family history		
Age of maternal walking	28.75	0.0071
Age of paternal walking	21.30	0.019
Age of siblings walking	18.36	0.049
Hypermobility in parents	0.73	NS
Hypermobility in siblings	0.12	NS
Rheumatic diseases	0.312	NS

Table 2 Classification of subjects into four clinical categories at stage I

	Group with hypermobile joints No (%)	Group without hypermobile joints No (%)	Total No (%)
Gross motor development			
Delayed	38 (30.2)	64 (10.9)	102 (14.3)
Normal	88 (69.8)	525 (89.1)	613 (85.7)
Total	126 (17.6)	589 (82.4)	715 (100)

Group with hypermobile joints v group without hypermobile joints $\chi^2=31.59$, $p=0.0001$

Table 3 Classification of subjects into four clinical categories at stage II

	Group with hypermobile joints No (%)	Group without hypermobile joints No (%)	Total No (%)
Gross motor development			
Delayed	7 (30.4)	18 (10.3)	25 (12.7)
Normal	16 (69.6)	156 (89.7)	172 (87.3)
Total	23 (30)	174 (100)	197 (100)

Group with hypermobile joints v group without hypermobile joints: $\chi^2=7.4$, $p=0.0065$

was not established, 223 fathers (39 of the group with hypermobility and 184 in the normal group) and 308 mothers (76 in the group with hypermobility and 332 in the normal group) were able to supply information regarding the age they attained walking. A significant association with their children's joint hypermobility was shown (table 4). A significant association was found between the sibling's walking age and the subject's joint hypermobility (table 4).

Discussion

The association between hypermobile joints and motor development in infancy has not been comprehensively evaluated. It is complicated by the fact that norms for the very young age group do not exist, and studies on the subject use criteria derived from older children. In this investigation the problem was circumvented by using age controlled subjects.

The results of this study confirm that in infants from the ages of 8 to 14 months, hypermobile joints are associated with a significantly increased incidence of motor delay. Specific joints were more often associated with the delay, namely excessive foot dorsiflexion, hip abduction, and elbow hyperextension (see definition). Furthermore, these three joints showed a synergistic rather than a additive effect.

Over the ensuing six months, 44 out of 58 (75.9%) of the infants with hypermobile joints lost their excessive mobility, 20 out of 24 (83.3%) of the infants with delayed development whose joints had become normal had caught up in motor development, whereas only six out of 11 (54.5%) of the infants with persistent joint hypermobility had achieved normal motor function. While these data did not reach significance, it may suggest that a biological relation does exist between hypermobile joints and motor development, and longer follow up may well have shown a larger percentage of motor catch up.

The benign nature of the phenomenon of hypermobile joints and motor development was suggested in the only study specifically studying this problem.⁴ This study found that a motor catch up occurred by the age of 3 years, while our investigation suggested that motor development became normal earlier.

Other investigations dealing with floppy infants and benign congenital hypotonia might have included a similar population to ours.^{9,10} These studies, however, were differently designed in that

they were descriptive, uncontrolled, and based on a broad clinical group who had been primarily referred for motor delay. The interesting association of bottom shuffling observed with hypotonia was also noted in our subjects.³ Unlike other studies we were unable to show a significant association of joint mobility with variables such as sex and ethnic origin.¹¹ An increased incidence of rheumatic diseases in other family members was not found.¹²

The implications of these results for clinical practice are that infants with a developmental profile showing motor delay as a sole manifestation, normal muscle strength and tendon reflexes, and increased joint mobility do constitute a clinical entity. This entity is associated with a favourable prognosis. Medical and neurophysiological investigations are not indicated and with appropriate counselling much anxiety and expense can be spared. It must be stressed that general clinical examination to exclude systemic disease is essential.

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Assessment of a new valveless infant ventilator

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SUMMARY A new valveless ventilator, which uses an air jet to provide the driving force for positive pressure ventilation, was used on 13 newborn babies (10 of very low birthweight) who had severe respiratory disease. The ventilator differs from 'true' jet ventilators in that its driving gas does not take part in gas exchange. Functionally it is a pressure pre-set, time-cycled ventilator, whose performance is characterised by the rapid and precise maintenance of both inspiratory and expiratory airway opening pressure. All the babies had progressively worsening respiratory failure (mean values of arterial $p\text{CO}_2$ were 9.46 kPa, with a pH of 7.14, and an inspired oxygen concentration of 52.5%) on conventional mechanical ventilation. On the new ventilator, with the same settings there was a dramatic and highly significant improvement within 20 to 30 minutes (mean values of arterial $p\text{CO}_2$ were 6.45 kPa, pH 7.26, and inspired oxygen concentration 35.7%). This improvement was maintained. The new ventilator represents an important advance in the management of babies with severe respiratory failure.

A new valveless ventilator has been developed at this hospital.^{1,2} The prototype, CW200, comprises two jets in a single tube (see fig 1). The driving jet delivers intermittent pulses of unconditioned gas, which provides the driving force for positive pressure ventilation, whereas the positive end expiratory pressure (PEEP) jet provides continuous gas flow that maintains positive pressure in the breathing circuit throughout the respiratory cycle. The gas

supply for these jets can be derived from any single convenient source: from either a piped supply or commercially available cylinders (air or oxygen). It need not be conditioned as it does not enter the patient's respiratory system. A low flow of an appropriate mixture of air and oxygen (roughly 2 l/minute for general neonatal use) that has been adequately warmed and humidified enters the breathing circuit close to the endotracheal tube. The

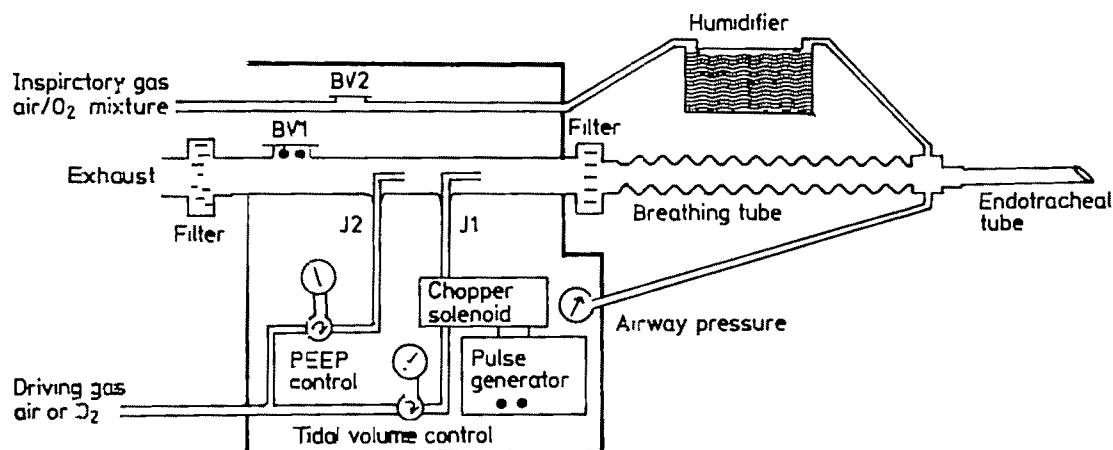


Fig 1 Schematic diagram of CW200 ventilator. J1 driving jet, J2 PEEP jet; BV1 and BV2 blow-off valves

driving jet functions like a pneumatic piston, it raises the pressure of the airway opening and drives the desired tidal volume of fresh respiratory gas collected in the breathing circuit into the patient's airways. The lung inflation pressure, and hence the tidal volume, is controlled by adjusting the pressure of the driving jet, independent of the fresh gas flow.

Functionally the CW200 is a pressure pre-set, time-cycled ventilator. It has no occluding valve or 'thumb like' device to limit gas exit from the circuit during the positive pressure (inspiratory) phase of the respiratory cycle. The breathing circuit is open to atmosphere at all times. It is capable of providing continuous positive airway pressure and intermittent positive pressure ventilation at low, normal, and high frequencies (range 0–200/minute). It differs from commercially available jet ventilators in that its driving jet is not placed at or near the patient's endotracheal tube and its output does not take part in gas exchange. Therefore tracheal complications and problems with conditioning of respiratory gas associated with true jet ventilators are not likely to occur.^{3–5}

The features and versatility of this ventilator would make it suitable for neonatal use. Because there are established mechanical ventilators in use in our unit we set out to evaluate its performance by

comparison with conventional ventilators. In preliminary observations we found it to be equivalent to existing mechanical ventilators in infants whose respiratory distress was easily controlled by conventional ventilator settings. We report our experience in the management of progressive respiratory failure in infants where conventional mechanical ventilation had failed.

Patients and methods

The performance of the CW200 was compared with other ventilators: the Vickers Neovent Model 90 (Vickers Medical, Basingstoke), SLE Newborn (SLE Ltd, Croydon), and the Sechrist Model IV 100B (EME, Brighton); the Neovent 90 is the most often used currently in our unit.

LABORATORY EVALUATION

Although the efficacy of different ventilators in neonatal respiratory support is not directly measurable in the laboratory, the mechanical properties of the different systems are likely to be reflected by the pattern of gas flow and pressure output. A standard breathing circuit, like that in use in our unit, was set up. A model lung of known compliance (1 ml/cm

Table 1 *Characteristics, sequelae, and outcome of infants with acute respiratory failure*

Patient No	Gestational age (weeks)	Birth weight (g)	Respiratory diagnosis before using CW200	Outcome	Respiratory sequelae (or necropsy results)
1	26	480	IRDS, PIE	Died at 2 weeks	(No necropsy)
2	29	550	IRDS, PIE	Died at 1 week	(Severe BPD, alveolar haemorrhage, tracheal lesions)
3	27	640	IRDS, PIE, pneumothoraces	Alive	BPD, O ₂ dependence for 2 months
4	28	720	IRDS	Alive	BPD, O ₂ dependence for 10 weeks
5	27	750	IRDS, PIE, BPD	Died at 2 weeks	(Severe BPD, broncho-pneumonia, tracheal excretion)
6	28	780	IRDS, PIE	Alive	O ₂ dependence for 8 weeks
7	30	910	IRDS, PIE, BPD	Died at 4 months	(No necropsy)
8	26	920	IRDS, PIE, pulmonary haemorrhage	Died at 2 days	(PIE with alveolar haemorrhage, extensive tracheal excretion)
9	28	950	IRDS	Alive	None
10	28	1000	IRDS, pneumothorax	Alive	O ₂ dependence for 6 weeks
11	31	1800	IRDS, unilateral PIE	Alive	None
12	41	2900	Meconium aspiration, Persistent fetal circulation	Alive	O ₂ dependence for 3 weeks
13	38	3190	Diaphragmatic hernia, Hypoplastic left lung, Persistent fetal circulation	Alive	None

IRDS idiopathic respiratory distress syndrome, PIE pulmonary interstitial emphysema, BPD: bronchopulmonary dysplasia.

H₂O) was connected in series with a resistance block (50 cm H₂O/l/second). It was filled with copper wool to ensure that changes occurring in the model were isothermal, 'intubated' with a size 2.5 mm Portex endotracheal tube, and connected to the ventilation circuit in series with an empty water trap (internal volume 55 ml) and a full humidifier (Vickers 90). The airway opening pressure and 'lung' pressure were recorded by pressure transducers (Bell Howell type 4-442, Bell and Howell Ltd, Wembley). A pneumotachograph (Cedar, Cardiokinetic Ltd, Manchester) was placed at the distal end of the endotracheal tube. Recordings of flow and pressure were obtained simultaneously on a two channel recorder (Devices, I.M. Intermedics, Welwyn Garden City). The different ventilators were studied in turn using the same breathing circuit and identical settings, which were arbitrarily chosen as follows: peak inspiratory pressure, 20 cm H₂O; positive end expiratory pressure (PEEP), 3 cm H₂O; gas flow rate, 7 l/minute (except for CW200 which was 2 l/minute); the inspiration:expiration ratio was 1:1. The rate of ventilation was increased in steps from 30 to 150/minute, except for Neovet 90 where a maximum rate of 90/minute was used. The pressure transducers and pneumotachograph were repeatedly calibrated during recording.

The Sechrist ventilator has an expiratory assist device. We used this to prevent high levels of circuit PEEP, with a fresh gas flow of 20 l/minute, to try to mimic the CW200.

CLINICAL EVALUATION

The criteria for trial on the CW200 ventilator included: PaCO₂ greater than 8 kPa or PaO₂ less than 4 kPa despite an inspired oxygen concentrations approaching 100%. Of the 13 babies studied consecutively on 15 occasions, 11 were preterm (gestational age 26–31 weeks) with respiratory distress syndrome and its complications, 10 had a birth weight under 1 kg, and two were term infants with severe pulmonary illness (table 1). All had been paralysed with pancuronium because of their severe respiratory failure. When the criteria for a trial on the CW200 were reached a change from the conventional ventilator was made. The ventilator settings were initially kept identical in order to facilitate comparison of ventilator performance. The pressure gauges of different models had previously been shown to give identical readings for pressures up to 50 cm H₂O with a water manometer. Arterial blood gases were measured immediately before and 20 minutes after the change.

Statistical analysis was by the paired sample *t* test.

Table 2. Ventilator settings, mean arterial pH, PaCO₂, and PaO₂/FiO₂ ratio in the hour before and after changing to the CW200 ventilator

Patient	Ventilator settings			pH	PaCO ₂ (kPa)		PaO ₂ /FiO ₂ (kPa)	
	PIP* (cm H ₂ O)	PEEP† (cm H ₂ O)	Rate (/minute)		Neovet	CW200	Neovet	CW200
3	28	3	60	7.2	7.3	9.5	6.3	10.0
4	27	4	70	7.1	7.2	10.3	7.5	13.3
5 (b)‡	32	3	70	7.2	7.24	8.6	6.9	10.1
6	26	4	70	7.1	7.3	9.0	5.7	12.0
7	30	2	75	7.0	7.05	10.5	7.7	3.6
8	28	2	60	7.34	7.41	5.3	4.2	4.0
9	24	3	55	7.0	7.0	10.9	8.9	21.9
11	30	4	75	7.0	7.15	14.2	9.3	17.0
12	26	3	40	7.24	7.5	6.3	3.7	3.3
13	24	2	70	7.25	7.46	6.9	4.9	3.4
				SLE	CW200	SLE	CW200	SLE
2 (a)‡	22	3	70	7.06	7.24	11.0	5.5	5.0
2 (b)‡	30	2	80	7.0	7.1	11.3	8.3	3.1
10	37	4	90	7.15	7.29	10.1	6.8	11.6
				Sechrist	CW200	Sechrist	CW200	Sechrist
1	26	2	80	7.19	7.26	8.4	7.1	8.0
5 (a)‡	32	4	100	7.24	7.42	9.6	4.0	6.7
Mean	28.1	3	7.1	7.14	7.26	9.46	6.45	
Probability				<0.001		<0.001		<0.01

*PIP=peak inspiratory pressure; †PEEP=positive end expiratory pressure.

‡Patients 2 and 5 were studied twice.

Results

LABORATORY EVALUATION

All three conventional ventilators produced similar pressure waveforms at frequencies of up to 90/minute. The inspiratory gas flow through the endotracheal tube and into the model lung was distinctly higher for the CW200 than for the other ventilators at identical settings (fig 2). Because of its design the CW200 produced a peak inspiratory gas flow rate of 6 l/minute, which was much higher than the fresh gas flow (2 l/minute). For the other conventional ventilators the peak inspiratory flow rate did not exceed 3 l/minute and was less than the fresh gas flow (7 l/minute). The high inspiratory gas flow for the CW200 meant that the time required to reach the target lung pressure, and therefore to deliver the desired tidal volume, was less than for conventional ventilators. This is reflected in the slope of the 'lung' pressure profile, giving it a 'square' pressure plateau at low frequencies and higher 'lung' pressure at high frequencies. The higher 'lung' pressure meant that,

for the same airway opening pressure, the CW200 delivered larger tidal volumes to the model lung at frequencies over 60/minute.

When we tried to mimic the CW200 by using a Sechrist ventilator at a fresh gas flow of 20 l/minute (with expiratory assist), although the circuit and 'lung' waveforms improved, they remained inferior. In particular, the pressure plateau was less 'square' and at 'lung' level, the fall in peak pressure at high frequencies was still greater than with the CW200.

CLINICAL EVALUATION

The CW200 ventilator was easily adapted to a standard breathing circuit as used on our ward. The mean arterial pH, carbon dioxide tension (PaCO_2) and ratio of oxygen tension to inspired oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) in the hour before the change from conventional ventilation to the CW200 was an index of the severity of respiratory failure (table 2). Using identical settings the change resulted in lowering of PaCO_2 and improvement in pH on every occasion, and increase in $\text{PaO}_2/\text{FiO}_2$ ratio on 13 out

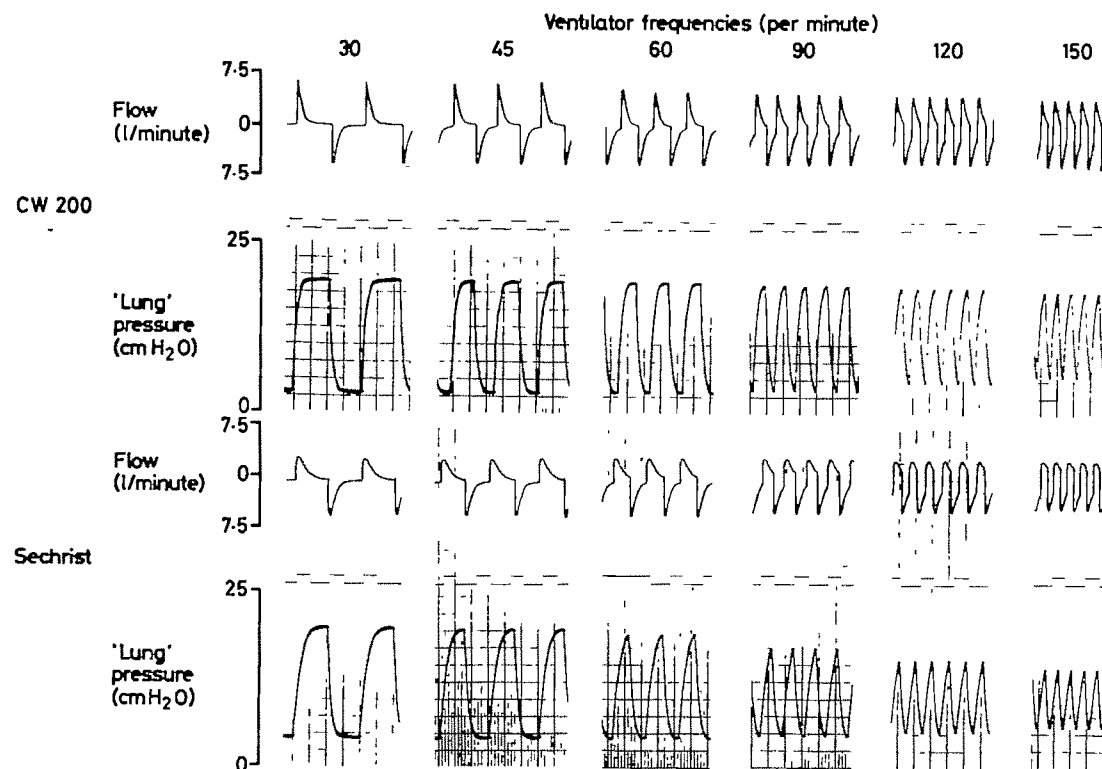


Fig 2 Gas flow and pressure in the model lung at several frequencies for the CW200 and Sechrist mechanical ventilators. The conventional ventilator failed to deliver the pre-set peak inspiratory pressure at a frequency of about 60/minute, the CW200 began to fail at about 90/minute. Inspiratory flow rate was higher at all frequencies with the CW200, expiratory flow rates were similar for both ventilators.

of 15 occasions. One of the two infants whose $\text{PaO}_2/\text{FiO}_2$ ratio fell had been hyperoxic (as well as hypercapnic) on conventional ventilation. In the other infant the small decline in oxygenation had to be compared with an appreciable improvement in PaCO_2 . The mean changes in PaCO_2 and $\text{PaO}_2/\text{FiO}_2$ were highly significant ($p < 0.001$ and < 0.01 , respectively). In the three cases in which the indication for change was persistent hypoxia (patients 8, 12, 13), improvement in oxygenation and $\text{PaO}_2/\text{FiO}_2$ ratio occurred in all three.

Five infants died, four in the neonatal period and one several months later due to chronic lung disease (bronchopulmonary dysplasia) (table 1). Necropsy performed on three infants showed evidence of hyaline membrane disease with interstitial emphysema (PIE); it confirmed alveolar haemorrhage in one infant (patient 8), and severe bronchopulmonary dysplasia with alveolar haemorrhage in the other two (patients 2 and 5). Tracheal lesions were evident in all three, ranging from partial desquamation and squamous metaplasia (patient 2) to severe excoriation (patients 5 and 8).

Eight infants developed signs of pulmonary air leaks (PIE and pneumothoraces). The occurrence of seven of them preceded the use of the CW200. A single pneumothorax occurred while patient 7 was being weaned off the CW200 ventilator. In addition, five infants developed chronic oxygen dependency for three weeks to four months after treatment on a ventilator. At the time of writing the youngest of the survivors in our series was 3 months old whereas the oldest was 13 months. None of them required ambulant oxygen treatment at home. There was no clinical evidence of upper airway problems among the survivors.

Discussion

This valveless ventilator is novel in that the driving force for lung inflation is provided for by a pneumatic piston. Provided that the fresh respiratory gas flow is more than twice the minute volume (greater than about 50 ml/kg/minute even at the highest frequencies of ventilation) and the internal volume of the breathing circuit between the driving jet and the endotracheal tube is more than the patient's tidal volume, the driving gas does not enter the patient's pulmonary system and therefore need not be conditioned. With the high peak inspiratory gas flow the CW200 is particularly advantageous at high frequencies of ventilation over 60/minute when the inspiratory time is inevitably short. In this study, it was assessed at relatively high frequencies (table 2), at which our laboratory studies had shown conventional ventilators to be failing (fig 2). At lower

frequencies the CW200 ventilator was no more effective than the existing ventilators.

For conventional ventilators the driving force for lung inflation is derived from the build up of pressure in the breathing circuit due to obstruction of the gas exit during the inspiratory phase while respiratory gas flow continues. During this time the gas in the breathing circuit is compressed, and then is discharged during the expiratory phase without actually contributing to the tidal gas exchange. This part of 'wasted' tidal volume is known as compressible volume. Its presence reduces the rate at which the target inspiratory pressure is reached at the onset of the inspiratory phase and therefore reduces the time available to deliver the tidal volume. Any leaks in the circuit will reduce the filling rate even more. Our experimental results suggested that the CW200 behaved as if the compressible volume were low. Its mode of operation would be more capable of overcoming minor leaks in the breathing circuit that were due to worn humidifier seals or endotracheal tube leakage. On the other hand, if there is a major leak in the fresh gas supply limb, or if the latter becomes accidentally disconnected, the unconditioned driving gas can inadvertently reach the patient's pulmonary system.

When attempts are made to use a conventional ventilator circuit at high frequencies, a higher gas flow into the breathing circuit is often used in order to compensate for large compressible volumes. This manoeuvre creates two further problems. Firstly, a high gas flow may exceed the output of the humidifier for conditioning of the respiratory gas; this leads to adverse consequences in the patient's airways.⁶ Secondly, the resistance to high gas flow through the exit valve may result in unacceptably high PEEP with its attendant undesirable effects. Although this circuit PEEP can be eliminated by an expiratory assist device, this has little effect on intrinsic PEEP at alveolar level.

With the CW200 ventilator the inflation pressure is not dependent on the flow rate of the fresh respiratory gas. Changes in ventilator pressure and frequency to meet the changing conditions of the baby can be made easily without any need for adjustment of fresh gas flow rate. The low fresh gas requirement means there is less wastage of respiratory gas and its conditioning is less dependent on the output of the humidifier, which may be less than adequate.⁷ Unlike the blow off valves of conventional ventilators whose escape pressure is not always precise the CW200 is open to atmosphere throughout the respiratory cycle. It is therefore intrinsically very safe, as the driving gas always flows back to atmosphere once the pre-set pressure in the breathing circuit is reached.

There are practical and ethical difficulties in designing a clinical trial of mechanical ventilation in conditions of acute respiratory failure. A cross over study was not possible as the response to the CW200 ventilator was so obvious in all cases that it would have been unethical to return these infants immediately to the conventional ventilation. Under these circumstances statistical analysis is of less value than the power of clinical observation. We cannot say whether, by using the CW200 from the outset, it might have been possible to prevent the development of severe respiratory failure. These infants, having shown improvement in blood gases, were kept on the CW200 until the ventilatory requirements could be sufficiently reduced and conventional ventilation was considered adequate, though two infants subsequently developed respiratory failure again after returning to conventional ventilation.

Our study has clearly shown that this new ventilator is superior to that of conventional pressure-limited time-cycled mechanical ventilators for infants with severe lung disease, especially when relatively large compressible volumes are present in the circuitry. The improvement in blood gases brought about by this ventilator was often followed by improvement in the patient's general condition, although five out of the 13 infants subsequently died. A further five who developed chronic oxygen dependency all had evidence of pulmonary interstitial emphysema before they were put on the CW200 ventilator. The high pulmonary complication and mortality rate in our series reflects the severity of their underlying lung disease. Only one new episode of air-leak occurred during the trial of this ventilator: as patient 7 was being weaned off the ventilator.

There have been numerous reports of local tracheal complications with neonatal high frequency jet ventilators.³⁻⁵ These are thought to be related to the fact that the 'jet' was close to the patient's airway and that adequate conditioning of the respiratory gas was difficult to maintain. Although the CW200 utilises an air jet to provide the force for lung inflation, it functions as a pneumatic piston. The output from the jet only pushes humidified respiratory gas into the breathing circuit and not directly into the patient's airway. Tracheal lesions, nevertheless, were observed in all three infants who underwent necropsy examination. This suggests that mechanical factors other than the inadequate conditioning of respiratory gas alone have a role in the aetiology of these lesions.

The improvement in blood gases brought about by the use of this new ventilator seems likely to be due to delivery of larger tidal volumes in these infants who, in general, had low lung compliance and high airways resistance.⁸ The waveforms shown in fig 2 suggest that at higher frequencies the mean 'lung' pressure was higher with the CW200; this could contribute to better oxygenation. It is also possible that high initial inspiratory gas flow rates, which we observed in the model lung, lead to improved CO₂ scavenging from the lungs.

In conclusion, our preliminary uncontrolled study has shown that this new valveless infant ventilator was more effective than conventional ventilators in providing mechanical ventilation to newborn babies in severe respiratory failure. Prospective, controlled studies will be needed to ascertain whether deteriorating respiratory failure can be prevented by its use, and to determine what influence it has on airway complications and mortality rate in such infants.

The expertise of the nursing staff of the neonatal unit was an essential factor in the success of the project. We are grateful to Professor JS Wigglesworth for his valuable comments.

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Observation of spontaneous respiratory interaction with artificial ventilation

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SUMMARY To compare the accuracy of clinical observation and detailed respiratory recordings in identifying infants at high risk of developing pneumothoraces 10 infants, with idiopathic respiratory distress syndrome, were studied at three different ventilator rates. All infants with synchronous respiration at fast rates were correctly identified by clinical observation. The clinical signs used to identify 'high risk' interactions—that is, active expiration and asynchronous breathing—were obvious respiratory efforts and a failure of improvement in oxygenation at increased rates. These criteria enabled correct identification of 'high risk' respiratory patterns on 15 (88%) of the 17 study occasions. These clinical criteria were then used as criteria for selective paralysis; no infant developed a pneumothorax during ventilation.

Spontaneous respiratory efforts during mechanical ventilation in preterm infants have been incriminated in the development of pneumothorax.^{1,2} Consequently attempts have been made to reduce the incidence of air leaks by using paralytic drugs; this was unfortunately unsuccessful.^{1–3} A possible explanation for this failure was the lack of selection of infants included in the studies. Preterm neonates breathe in one of four distinct interactions with artificial ventilation.⁴ Two of these—synchronous respiration⁵ and provoked augmented inspirations⁶—are advantageous. Inhibition of such interactions by paralytic drugs, which reduces the positive contribution to gas exchange, could increase the need for ventilation and hence result in pneumothoraces. Only one pattern of respiration—active expiration—was found to be significantly associated with the development of pneumothorax.⁴ When infants showing only this interaction were paralysed a highly significant reduction in the incidence of air leaks resulted.⁷

Detection of active expiration needed sophisticated respiratory recordings utilising expensive equipment and expertise to obtain the recordings and for their interpretation.⁷ It was thus desirable to be able to identify accurately such high risk infants by clinical observation alone. This was attempted in a subsequent trial.⁸ The criteria for selection for paralysis included 'struggling against the ventilator.' Unfortunately, although selective paralysis again produced a significant reduction in the incidence of

air leaks,⁸ the magnitude of effect was less noticeable than in the previous study.⁷ This was possibly due to the less accurate method of detection of high risk infants.

We had previously noticed that comparison of the respiratory efforts of infants at two different ventilator rates enabled more reliable diagnosis of their interaction with artificial ventilation. The accuracy was improved if changes in transcutaneous oxygen concentrations were also considered. Infants whose respiratory efforts became less obvious at the faster rate in association with an upwards trend in transcutaneous oxygen concentrations were accurately described by the nurses as fighting the ventilator at the lower rate and synchronously respiring at the increased frequency. The purpose of the present study was to investigate whether, by studying infants at a series of ventilator rates, it was possible by clinical observation alone to identify correctly infants who would benefit from paralysis.

Patients and methods

Ten infants with a clinical diagnosis of the idiopathic respiratory distress syndrome were each studied at three different ventilator rates. Their mean birth weight was 1037 g (range 630–1500 g), and their mean gestational age was 27.5 weeks (range 25–31 weeks). Their mean age at the time of study was 19 hours and all were less than 3 days old. The infants were receiving intermittent positive pressure

ventilation (IPPV) by Sechrist ventilators. Before the study the ventilator rate was 30 breaths/minute. No infant had a pneumothorax or was receiving paralysing or sedating drugs at the time of the study.

Each infant was studied in his or her incubator while receiving full intensive care. The infants were ventilated at a succession of rates of 30, 60, 30, 120, and 30/minute, each rate being maintained for 20 minutes. There were no other changes in ventilator settings, mean airway pressure (MAP) was kept constant at the increased rate by altering flow as necessary. At the initial period of 30 breaths/minute and at 60 and 120 breaths/minute the infant's respiratory interaction to ventilator inflation was recorded independently by two observers. One observer (AG) used detailed respiratory measurements⁹ and the other (research sister FG) used clinical observation and trends in transcutaneous oxygen. The two observers were unaware of each others results

Respiratory efforts were recorded by an oesophageal balloon and catheter system attached to a pressure transducer (Validyne range ± 50 cm H₂O). A pneumotachograph (Mercury F10L) attached to a pressure transducer (Validyne range ± 2 cm H₂O) was placed between the endotracheal tube and ventilator circuit and recorded flow changes both due to the infant and the ventilator. This signal was electronically integrated to give volume (Integrator model No 13-4615-70). Ventilator pressure changes were recorded from the infant's side of the pneumotachograph (Validyne pressure transducer range ± 50 cm H₂O). All the pressure transducers had a similar frequency of response, 63% rise time of 6 milliseconds, shown by a balloon burst experiment. Ventilator and oesophageal pressure, flow and volume changes were all recorded simultaneously on a Polygraph (Gould 2800S). The infant's respiratory interaction with the ventilator was determined by analysis of the last 10 minute portion of the 20 minute recording at each ventilator rate.

The observer blind to the respiratory recordings but aware of the ventilator rate made a clinical judgment of the infant's interaction with positive pressure inflation. This was based on observing the number of respiratory efforts in relation to ventilator frequency, the direction and magnitude of chest wall movement with relation to the ventilator cycle, and changes in transcutaneous oxygen with alteration in ventilator rate. Transcutaneous oxygen was monitored (Draeger Oxymeter) throughout the study. The trend of change in transcutaneous oxygen was assessed by comparison, at each ventilator rate, of the average recording of the first and last five minutes of the 20 minute period.

At each ventilator rate the infant's dominant respiratory interaction with the ventilator was placed into one of three groups. The dominant interaction was that shown on more than 80% of ventilator breaths.

(1) SYNCHRONY

- (i) Respiratory recording: spontaneous inspiratory efforts coincided with the start of every or every second ventilator inflation.
- (ii) Clinical observation: chest wall movement (upward deflection) occurred synchronously with ventilator inflation. As the rate was increased it became more difficult to distinguish chest wall movement due to the infant's respiratory efforts or positive pressure inflation. Supportive evidence was an upwards trend in transcutaneous oxygen partial pressure at the increased rate.

(2) ACTIVE EXPIRATION

- (i) Respiratory recording: during positive pressure inflation the oesophageal pressure recording showed the infant to be in expiration and this was associated with an expiratory flow.⁷
- (ii) Clinical observation: poor chest wall expansion or a downward movement of the chest wall during positive pressure inflation. Supportive evidence was a failure to improve transcutaneous oxygen partial pressure by increasing ventilator rate.

(3) ASYNCHRONY

- (i) Respiratory recording: the infant exhibited neither synchrony nor active expiration and/or spontaneous breaths occurred through out the ventilator cycle.
- (ii) Clinical observation: spontaneous respiratory efforts had a poor relation to the timing of ventilator inflation. Despite the increasing ventilator rate the infant's respiratory efforts were obvious and often distinct from chest wall movement due to positive pressure inflation. Supportive evidence was that an increased ventilator rate was not associated with an improvement in transcutaneous oxygen partial pressure.

To assess the accuracy of clinical observation in determination of the type of respiratory interaction, at the end of the trial, comparison was made of the results of the two observers for the 10 infants at each ventilator rate.

On completion of the study infants with synchronous respiration were subsequently ventilated at the slowest rate at which this was achieved.¹⁰ At fast

rates both asynchrony and active expiration had previously been used successfully as criteria for selective paralysis to reduce the incidence of pneumothoraces.¹⁰ As a consequence those infants continuing to show either interaction at increased ventilator frequencies, shown by respiratory recordings, were paralysed¹¹ and subsequently ventilated at 60 breaths/minute.

Results

Respiratory recordings confirmed that most infants (eight out of 10) were actively expiring at the slowest rate. As ventilator rate was increased infants tended to breathe in synchrony with their ventilator; seven out of 10 at 120/minute (table 1).

When the results from the studies at all three ventilator rates were examined, clinical observation correctly identified all 13 occasions on which infants were synchronously respiring with their ventilator (table 2). No infant breathing either synchronously or asynchronously during ventilation was incorrectly identified as actively expiring by clinical observation. A change to synchronous respiration at the

increased frequency was associated in all cases with an improvement in transcutaneous oxygen concentration (mean change 12 mm Hg, range 8–22).

Or only five of 13 occasions during which infants were actively expiring was the interaction correctly identified by clinical observation, giving a sensitivity of 38% (table 2). At the slowest ventilator rate of 30 breaths/minute, five of the eight infants were correctly identified as actively expiring. At the faster ventilator rates, 60 and 120 breaths/minute, no infant actively expiring was identified by clinical observation, but six of the seven infants were labelled as asynchronous. Inclusion of asynchrony and active expiration as one group improved the sensitivity of clinical observation to 88%. Clinical observation correctly identified infants breathing in one of these two interactions on 15 of 17 occasions (table 2).

Three infants failed to achieve synchrony at any ventilator rate. As they continued to breathe asynchronously or actively expired they were paralysed after completion of the study. None of the other seven infants were paralysed during subsequent ventilation and during the acute phase of their respiratory illness the ventilator rate remained unchanged. Although non-paralysed infants were not restudied, as none of the 10 infants developed a pneumothorax, this suggests that if the appropriate fast rate of ventilation is chosen synchronous respiration is a stable interaction during the acute phase of the respiratory illness.

Table 1 *Spontaneous respiratory interaction with positive pressure ventilation at different ventilator rates*

	Ventilator rate (breaths/minute)		
	30	60	120
(a) Respiratory recordings			
Active expiration	8	4	1
Synchrony	0	6	7
Asynchrony	2	0	2
(b) Clinical observation			
Active expiration	5	0	0
Synchrony	1	7	7
Asynchrony	4	3	3

The number of study occasions on which particular interaction was either (a) recorded or (b) observed is given at each ventilator rate.

Table 2 *Comparison of the two observers' results at each ventilator rate*

	Ventilator rate (breaths/minute)		
	30	60	120
Interaction			
Active expiration	5 (8)	0 (-)	0 (1)
Active expiration or asynchrony	9 (10)	3 (-)	3 (3)
Synchrony	1 (0)	7 (+)	7 (7)

Observations made with the help of respiratory recordings are in parentheses; observations based on respiratory recordings are not in parentheses.

Discussion

These results confirm that active expiration is common particularly among immature infants who are ventilated at slow rates.⁷ When the ventilator rate is increased synchronous respiration tends to be induced and active expiration prevented.^{10, 12} The faster ventilator rates more closely mimic the spontaneous breathing frequency of infants suffering from the respiratory distress syndrome and hence are more likely to induce synchronous respiration.¹³

Clinical detection of active expiration was only partially successful and particularly unsuccessful at faster rates. If, however, active expiration and asynchrony were classified together, clinical observation correctly identified infants belonging to this group on 15 (88%) of 17 occasions and no infant was incorrectly placed in this combined group. Thus if the criteria used for paralysis was a clinical observation of either asynchrony or active expiration, this would ensure inclusion of most infants at highest risk of developing pneumothoraces; but equally importantly no infant would unnecessarily be paralysed.

Clinical detection of respiratory interaction was facilitated by observing trends in transcutaneous oxygen partial pressure with increased ventilator rate. All infants changing to synchronous respiration at the faster frequency had improvements in transcutaneous oxygen, as would have been predicted from our earlier results.⁵ The combination of 'obvious' respiratory efforts and a lack of improvement in transcutaneous oxygen at increased rates improved the accuracy of detection of infants asynchronous or actively expiring at the increased frequency and thus at high risk of developing pneumothoraces. These results suggest clinical observation of the infant's respiratory efforts and trends in transcutaneous oxygen monitoring, providing the infant is studied at different ventilator rates, can readily identify most infants who would benefit from paralysis.

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Increasing medical burden of child abuse

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SUMMARY During the decade January 1976 to December 1985, as a result of increased public awareness, the numbers of reported (but not proved) cases of abuse to children living in South Birmingham increased thirtyfold; the incidence of detected and proved cases of abuse increased fourfold. The increase was principally due to bruises, scalds, and neglect. The numbers of serious fractures and brain injuries did not increase. The first case of sexual abuse was reported in 1981 and this was followed by a subsequent rise in the detection rate. The combination of increased reporting, increased incidence of proved abuse, and the necessity for increased supervision of families and intervention has created a serious burden on the child health services that may necessitate a reduction in services to other children. Alternative ways of tackling the problems of child abuse may have to be introduced, but they may have unwelcome consequences.

Violence against infants and children has been recorded throughout history. Darwin postulated that one could correlate the beginning of human civilisation with the recording of infanticide.¹ The reported incidence of child abuse varies with definition and is thought to be always underestimated. It is generally accepted in Britain that one in 1000 children is severely injured and one in 10 000 killed by child abuse each year.²

The public started to become aware of the size of the problem after Kerpe used the intentionally emotive phrase 'battered baby syndrome' in 1962.³ Despite better detection rates and attempted prevention, however, reports of fatal non-accidental injuries from the general public gave the impression that there had been an increase in severe physical abuse that could be correlated with changing social conditions.

Child abuse is often so horrifying that there is a natural public reaction to divert services to investigate, treat, or prevent it. With finite resources this cannot be done without reducing or redeploying other children's health services. A discussion document from the Department of Health and Social Security (DHSS) recommended changes in procedure but suggested that these could be achieved within current staffing and budget limits.⁴ The present study was undertaken to find out if, in one urban health district, there had been an objective change in the range of child abuse and also to see if there had been any changes in the type of medical work load.

Subjects and methods

All available records were examined of abused children living in the area covered by the South Birmingham Health Authority that had been detected for the period January 1976 to December 1985. These records were held by community health doctors, health visitors, paediatric wards, the National Society for the Prevention of Cruelty to Children (NSPCC), and the social services. Children first identified in other health districts were included, but residents from outside the area but identified within it were not. Details of the referring source, the child's age, sex, social background, and injuries were abstracted. Incidences are presented as the number of cases per thousand children aged 0-15 living in the area.

Cases of injuries that were not adequately explained but which were not proved to be abuse, and unsubstantiated reports from the public about possible abuse, were not included. Because of the seriousness of a positive diagnosis for the family, and a missed diagnosis for professionals, all these cases took a considerable time to investigate. The number of cases increased from 15-30 a year in the 1970s, to 450 in 1986. About half were found to be incorrect or malicious after initial inquiries—for example, a child was anonymously referred as being systematically starved when (after lengthy enquiries) it transpired that the mother's sister was annoyed at not having received a birthday card and

knew that a referral alleging child abuse would inconvenience the family.

Results

The numbers of children abused, total numbers at risk, and annual incidences are shown in table 1. Over the decade there was a fourfold increase in cases of proved abuse. This occurred at a time when the total population of children was falling. During the same period there was an even greater increase

in the associated medical workload, as indicated indirectly by the increase in the number of case conferences. Each lasted one to two hours in addition to the time taken in preparation and follow up, and was attended by an average of four health authority employees.

Table 2 shows that there has been no major change in the pattern of injury; soft tissue injuries (including bruises and burns) still constitute most of the abuse. The numbers of severe injuries (including fractures and brain damage) have not increased but cases of neglect have increased from two to 22. The first case of sexual abuse was reported in 1981, and there has been a subsequent rise, though the incidence is still below that reported from other parts of the country.⁵ It is not clear yet whether the actual incidence or the rate of detection is low. There is local anxiety about a perceived failure to achieve some notional national norm. Schools and nurseries have responded to a training programme with an increasing, and increasingly early, rate of detection. Health visitors continue to play a vital part in the detection of the abuse of preschool children.

Table 3 shows the biological and social characteristics of the abused children. Both sexes were equally prone to abuse. In keeping with other

Table 1 *Numbers and rates of abused children within South Birmingham Health Authority 1976-85*

Year	Child population	No of cases of abuse	Rate	No of conferences
1976	59 300	22	0.37	29
1977	59 800	22	0.37	28
1978	56 000	18	0.32	31
1979	54 100	22	0.41	52
1980	53 000	27	0.51	52
1981	51 414	23	0.45	40
1982	51 545	16	0.31	28
1983	50 952	25	0.49	46
1984	50 457	61	1.21	123
1985	50 145	83	1.66	154

Table 2 *Type of injury and source of detection*

	Year 1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
Type of injury										
Soft tissue	16	13	11	16	16	13	6	14	33	51
Serious	4	3	3	3	1	1	3	3	4	5
Neglect	2	6	4	3	10	8	6	8	20	22
Sexual abuse	—	—	—	—	—	1	1	—	4	5
Source										
School	8	7	9	5	6	8	4	3	22	36
Social worker	—	—	—	1	1	2	1	7	4	7
Health visitor	3	4	2	5	4	4	4	6	10	11
Hospital	7	5	6	5	8	6	4	4	19	10
Other	4	6	1	6	8	3	3	5	6	18

Table 3 *Social and biological characteristics of abused children*

	Year 1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
Boys	15	10	7	15	13	9	11	13	31	42
Girls	7	12	11	7	14	14	5	12	30	41
Age <4 years	9	13	8	14	14	12	9	16	29	28
First child	13	10	11	14	14	14	11	11	42	39
Single parent	6	7	4	5	7	5	3	10	21	23
Mother aged <25 years*	8/17	9/13	10	17	15/23	12/17	9/12	10	19/37	23/58

*Mother's age not always recorded

studies,^{6,7} the first child in a young family is more likely to be abused, especially under the age of 3.

Discussion

The fourfold increase in the incidence of proved child abuse in South Birmingham during the past decade is partly associated with increasing public awareness and reporting and it has occurred when the total population of children was falling. This may indicate a worrying increase in child abuse that may get even worse as the birth rate increases. Unemployment within the area increased by 50% between 1981 and 1986. There was a disproportionately high rate of households with single parents, and the illegitimate birth rate was 27% of all births. High migration increases the difficulty of maintaining contact with families at risk and each new family takes time to identify and understand. Even without the problems of child abuse or neglect, such social deprivation places a considerable burden on staff working in child health.

The workload associated with the follow up of cases of proved abuse has led to some of our health visitors now spending up to 25% of their working week on cases of child abuse. On average, 10% of our health visitors' time is spent on investigating or monitoring such cases. This type of work is unpleasant and may be changing health visitors into social policemen/women. The relative decrease in the number of serious injuries (table 2) may reflect at least partially the success of the policy of increased support for high risk families, especially as a consequence of the 1980 Children and Young Persons Act. A similar fall in cases of serious abuse was reported from South Glamorgan between 1972 and 1982⁸ which contrasts with the experience in the north west of the United States of America, where there was an increase in serious injuries during the early 1970s.⁹ A report from Bradford however, was pessimistic about the effectiveness of the current policy of intervention.¹⁰

Successful prevention requires recognition of the circumstances which lead families to deprivation and abuse. There are some who believe that the welfare state has created a subclass that can only better its lot by sinking further in order to obtain additional provision.¹¹ Certainly the quickest way to get a child into some municipal nurseries is by holding an abuse case conference. Alternative methods of rectifying poor parent care are urgently required. Reproduction is our main biological function and it is therefore of concern that many educational authorities assume that the skills of parenthood are instinctive and do not need to be taught. More and better use could also be made of contact with

medical and other professional people when there is not a crisis. During the antenatal period mothers are particularly receptive to advice about child care; perhaps antenatal classes should devote more time to teaching them about caring for the baby and less to the actual conduct of the confinement.

It may also be necessary to reconsider whether the accepted (sociological) model of child abuse is correct. An alternative biological explanation has statistical support.¹² Lower animals are more kindly disposed to their genetic kin than towards others of their species, and it is similar with humans. The ratio of unrelated to related assailants in murder cases is 10:1. Children are most often abused or killed by a non-blood relative, infanticide is rare, and not dependent on the mother's marital state, but is inversely related to her age.¹² Older mothers may be restrained from abusing their children because of their decreasing fertility. Infanticide and child abuse may be a primeval response to unpropitious circumstances. Lactating hamsters eat their young if the nest is disturbed.

If this biological model is correct then there are two immediate consequences. Firstly, the environment in which young unsupported families are housed must assume a higher priority but, so that this is not misused, such provision might include removal of some parental rights. Secondly, those children who cannot be discouraged from indulging in sexual experience must have ready access to contraception until such time as their emotional and biological development is in step.

In no condition have the medical and social models shown more limitation than in the treatment of abused children. Those who are least able to protect themselves continue to suffer. 'Even without damage from trauma, even without the associated effects of poverty, deprivation, undernutrition or neglect, the child cannot be expected to thrive in a house in which fear of bodily harm is an unrelenting spectre'.¹³ These children may one day become parents themselves. It is of great concern that this cycle of deprivation and abuse appears to be self-perpetuating and that mechanisms for this perpetuation appear to be enshrined within our current statutes of child care.

Increasing detection and support of abused children cannot be done with current staffing levels and budget limits unless other aspects of child care are ignored.

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Cleft palate and glue ear

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SUMMARY The invariable presence of otitis media with effusion in children with cleft palate aged from 2 to 20 months is confirmed in a prospective trial, and the diagnosis was made in each case by myringotomy. Treatment planning should take account of this, and long term ventilation of at least one ear seems to be mandatory in order to correct bilateral congenital deafness. Close cooperation between otologist and plastic surgeon is essential for diagnosis and treatment of otitis media in these patients.

The association between hearing loss and a cleft palate is well established.¹⁻⁴ The hearing loss observed in adults with cleft palate is usually conductive and related to scarring, adhesions, and perforations of the tympanic membrane. It is suggested that these symptoms are late sequelae of untreated or unresolved middle ear effusions.^{5,6} Much recent research centres on otological problems in children and infants with cleft palate. Various incidences of otitis media (OME) have been recorded,^{7,8} however, the precise incidence is not established. This is largely due to methodological differences in the studies concerned, particularly the use of different techniques to assess middle ear function. The effects of OME on hearing, speech, and intellectual development have also been the subject of clinical research.^{9,10} Thus at the present time it seems important to establish the incidence of OME in children with cleft palate, and it is important to decide whether early and active treatment of middle ear effusions will prevent or minimise the long term otological and developmental sequelae.

In 1981 a multicentre prospective trial was established at four hospitals with both plastic surgical and ear, nose, and throat units: University College Hospital, London, The Hospitals for Sick Children (Great Ormond Street, and Queen Elizabeth Hospital, Hackney), and the Queen Victoria Hospital, East Grinstead. In this trial myringotomy was performed for all children with cleft palate irrespective of previous otological findings. When OME was confirmed one ear only was ventilated, thus each child provided a ventilated and a non-ventilated (control) ear. The main aim of the trial was to

answer these questions: (1) What is the incidence of OME in cleft palate children? (2) What is the effect of palate repair on subsequent eustachian tube function? (3) Are there any advantages in early long term ventilation of the middle ear? This report concentrates on the first of these questions only.

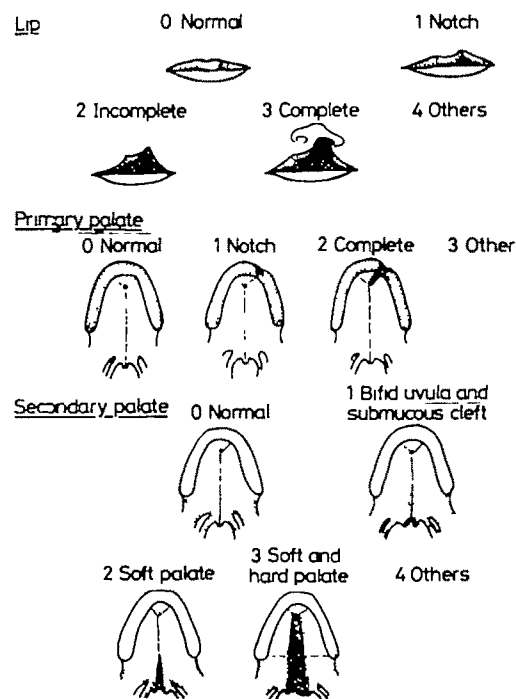


Fig 1 Cleft defects.

Patients and methods

Cooperative otological and plastic surgery was performed at each participating hospital to minimise admissions and anaesthetics. Investigations included a formal assessment of cleft defect at presentation (fig 1), otoscopic inspection of tympanic membranes and impedance measurement, otoscopic examination with a microscope, and bilateral myringotomy under anaesthetic. All observations were documented and a database established using a dBASE 11 data management system and an Apple 11E computer.

With parental consent children with cleft palate who were treated in the plastic surgery departments of the above hospitals were registered and entered into the trial, some at birth, others just before plastic surgery.

The child attended the ear, nose, and throat outpatient clinic the day before surgery, for otoscopy and tympanometry. (The type of impedance meter varied: at the Queen Victoria Hospital an American AR85 was available, and at the other three hospitals a Graystad GS1 28 was used.) The next day, under general anaesthetic, both ears were

inspected with an operating microscope, and myringotomy and aspiration of middle ear contents by microsuction was performed. With OME confirmed by aspiration a long term ventilation tube (the protocol recommended a Goode 'T' tube) was inserted in one ear at random. For children re-admitted for a second examination with a microscope the above procedure was repeated for the non-ventilated (control) ear, and patency of the in situ ventilation tube confirmed.

Otological follow up was maintained to assess the patency of the ventilation tube, the state of the ear undergoing myringotomy alone, and to monitor hearing. Early liaison with a speech therapist ensured subsequent speech and language assessment. The trial protocol is outlined in fig 2.

Results

By July 1986, 112 children had been registered in the study. Fifty five children had undergone examination with a microscope and bilateral myringotomy: 15 at the time of lip repair, 34 at palate repair, and six as a separate procedure (see fig 2). Six children had a second examination with myringotomy of the

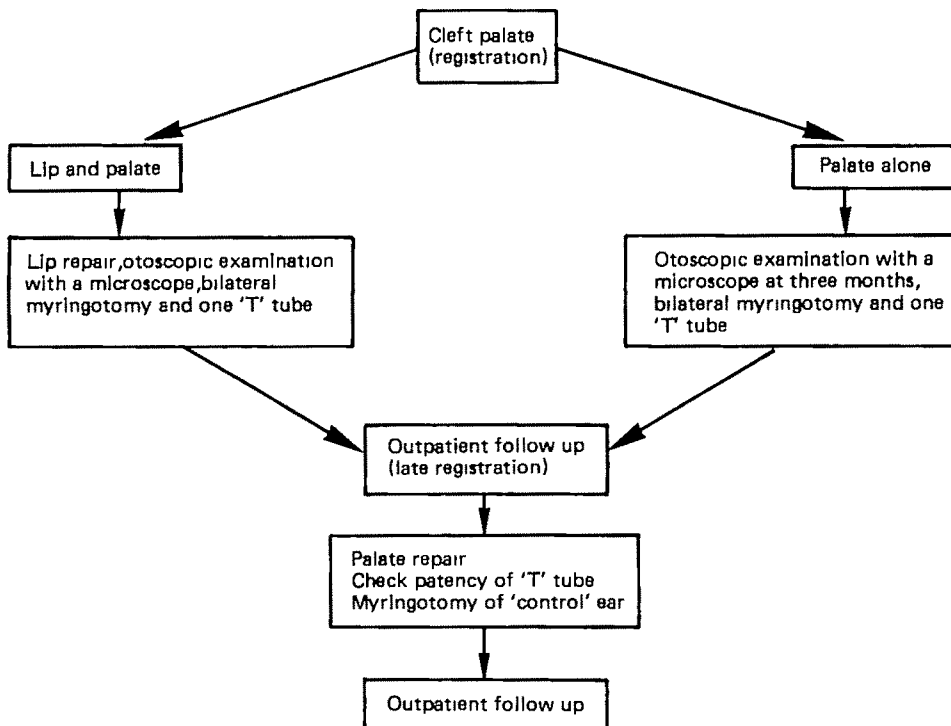


Fig 2 Trial protocol *With late registration bilateral myringotomy and ventilation of one ear were performed at palate repair.

Table Age at myringotomy and operations in 55 children

Age in months	—	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Nos of children	—	1	12	6	—	—	2	—	3	3	1	8	5	3	7	5	1	—	1	1

'control' (non-ventilated) ear. Thus observations were recorded for 116 ears (bilaterally at 55 operations and unilaterally at 11 operations). The table shows the age at myringotomy. Age at surgical repair varied between hospitals and surgeons, but on average lip repair was at 3.3 months (range 2-4 months) and palate repair at 13 months (range 7-17 months).

The diagnostic rate of tympanometry in 51 ears (55 children) was: normal peaked curve, four (7.3%) and flat (type E) curve, 47 (92.2%). Wax occluded the external auditory canal in 42 out of the 116 ears, which prevented reliable observation. The small number of ears effectively tested by impedance measurement reflects practical difficulties associated with this technique. Tympanometry accurately predicted findings at myringotomy for 46 out of 51 ears.

On examination with an operating microscope otoscopic findings on 115 ears in 55 children (two observations were made in six ears) were: normal tympanic membrane, five ears (4.3%) and diagnostic appearance of OME, 110 ears (95.7%). Some children with apparently normal tympanic membranes had effusions at myringotomy; for two patients (four ears) the appearance of the tympanic membranes was not documented. When confirmed by myringotomy there was a high incidence of OME in 113 of the 116 ears (97.4%). Three middle ears contained no fluid.

The type of fluid aspirated at myringotomy in the 113 ears with OME was: serous, in 11 ears (9.7%); mucoid, in 23 ears (20.4%); 'glue', in 57 ears (50.4%); and it was not recorded in 22 ears (19.5%). The distribution was similar to that seen in children without a cleft palate who have OME.

Discussion

In this typical sample of children with cleft palate myringotomies were performed irrespective of previous otological findings, and were not limited to those children with symptoms. The age of objective diagnosis of OME by myringotomy, and the 97% incidence reported here, merit careful consideration. Furthermore, had any of the three 'dry' ears contained serous fluid capable of displacement under general anaesthetic the incidence of OME would have been even higher.

Too-Chung has suggested the middle ear is

aerated from birth until 4 months of age in children with cleft palate.¹¹ This claim is not supported by our evidence. In this study no myringotomies were performed before 2 months of age, and therefore the state of the middle ear at birth cannot be inferred. OME was confirmed, however, by myringotomy from 2 months onwards; this supports earlier findings that OME is present in very young children with cleft palate, and as it occurs throughout the observed age range spontaneous resolution seems unlikely.⁸ In addition, Too-Chung's observations rely on tympanometry, which may not be the most appropriate technique for assessment of middle ear function in very small children.

In this study the observation rate for tympanometry was disappointing. For 55 children with cleft palate, only 51 ears were effectively tested with an impedance meter. In our experience wax occluding the external auditory canal, a narrow pliable ear canal, or an uncooperative child all mitigate against successful assessment. In addition impedance meters and technical help were not always available at short notice. Thus despite a 90% diagnostic reliability many children simply could not be tested. By contrast the observation rate for examination with an operating microscope was 100%.

Many authorities have placed great emphasis on impedance testing to confirm or exclude OME in children with cleft palate and a wide range of incidences is reported. Unfortunately many of these series are retrospective and the reliability of this technique cannot be confirmed. Although a dedicated impedance meter and technical help in each plastic surgery unit would have improved the observation rate achieved in this study, for the reasons listed above, we conclude that accurate diagnosis of OME must rely on otoscopy followed by myringotomy in all children with cleft palate.

The advantages and disadvantages of inserting grommets to treat OME in normal children is currently a matter of heated debate.^{12, 13} The precise aetiology of OME remains uncertain although Eustachian tube function is strongly implicated in children with cleft palate.¹⁴ Medical treatment of persisting OME is disappointing. In consequence reliable restoration of hearing by surgical intervention and insertion of grommets is favoured and accounts for this procedure being the most common paediatric operation performed in both the United Kingdom and North America.

In children with a cleft palate the clinical picture of OME from birth or shortly before is very different from that found in children without a cleft palate where the peak incidence is between 3 and 6 years of age. For the former group the onset of OME and associated hearing loss precedes language acquisition and early speech development. Furthermore the condition seems to persist throughout infancy and early childhood. Thus in addition to risks of long term otological sequelae of OME, the untreated child with cleft palate may also suffer language, intellectual, and emotional disability as a consequence of both early hearing loss and original deformity.⁹ Adenoidectomy can play no part in treatment of children with cleft palate for fear of further impairing velopharyngeal competence or exaggerating rhinolalia aperta, and it is also hazardous in very young children. Active treatment of deafness must therefore include ventilation of the middle ear on one or both sides, but should logically only follow accurate diagnosis.

If parents accept the need for surgical diagnosis and treatment of OME this should not require separate anaesthesia because it can be linked to surgical repair of the lip or palate, or both, if close cooperation between surgeons is achieved. Symptomatic OME necessitating myringotomy before or after plastic surgery may need a further anaesthetic, but in our experience the number of children requiring this will be small.

The Shepard grommet may not be the most suitable device for maintaining middle ear aeration in children with cleft palate because it will be extruded on average at 6.6 months,¹⁵ and recurrent OME will necessitate repeated anaesthetics. The Goode T tube, on the other hand, has been shown to remain in situ for substantially longer periods without causing additional tympanic membrane or middle ear complications.¹⁶ Long term ventilation with this type of tube should reduce the incidence of the late sequelae of OME including adhesive otitis, ossicular damage, and cholesteatoma, all of which are particularly evident in untreated children with cleft palate.³ It is hoped that long term follow up in this trial will yield additional information on this matter.

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Improved diabetic control in a district general hospital clinic

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SUMMARY A clinic for diabetic children was established in 1983 in a district general hospital to coordinate the changeover to a standard 100 unit insulin regimen. The children's progress was monitored for the next three years. Glycated haemoglobin A_{1c} (HbA_{1c}), measured at the same time each year, fell from a mean (SD) of 15.8 (4.7)% to 9.9 (2.6)% over the three years. A similar degree of improvement was seen when newly diagnosed patients were excluded from the analysis. This improvement was associated with a rise in mean (SD) insulin dosage from 0.89 (0.29) U/kg/day to 1.17 (0.35) U/kg/day. Good control was achieved more easily in children who had been diabetic for less than two years and in those who were prepubertal (particularly boys). A combination of isophane and soluble insulin appeared to be more effective than zinc and soluble insulin in maintaining good control. Ten complications of diabetes were noted in eight patients from 5.2 to 12.4 years after diagnosis.

These results show that setting up a diabetic clinic for children in a district general hospital had a beneficial effect on the quality of diabetic control and such improvement may help to reduce the incidence of diabetic complications.

During the past decade it has become accepted that improving the quality of diabetic control may delay the onset of complications as well as improving the wellbeing of patients without complications. In March 1983 insulins of a standard 100 unit strength (U100) were introduced in Great Britain partly to simplify insulin dosages and partly to avoid the confusion which had arisen from having two insulin strengths available (40 units and 80 units).

Changing patients from 40 unit and 80 unit regimens to U100 insulin in this department was undertaken by one person with a particular interest in diabetes. In setting up a clinic for diabetic children the opportunity was taken to examine the quality of control at the time of admission and to study any changes during the next three years.

Patients and methods

All diabetic children under the care of the consultants at East Birmingham and Solihull hospitals were admitted to the clinic. All patients remained nominally under the care of their original consultant who was kept informed of their progress. Newly diagnosed patients were also admitted to the clinic and followed up in the same way.

At each visit patients were measured using a Harpenden stadiometer and weighed. A sample of urine was taken and tested for the presence of protein, glucose, and ketones. At least once a year all patients had a full examination to exclude the presence of cataracts, retinal changes, hypertension, hepatomegaly, peripheral neuropathy and vascular disease. Pubertal development was assessed by the method of Tanner¹ and with a Prader orchidometer.² Puberty was considered to have occurred in girls if the menarche had been reached (mean age in normal children 13.0 years) and pubic hair of Tanner stage IV achieved (mean age in normal children 12.9 years), and in boys if they had pubic hair of Tanner stage IV (mean age in normal children 14.5 years) and testicular volumes of more than 12 ml (mean age in normal children 14.4 years).

C-peptide concentrations were not measured. The prevalence of residual β cell function, however, is almost 100% in patients who have had diabetes for less than two years^{3,4} but declines thereafter. Patients were therefore defined as 'established diabetics' if the diagnosis had been made more than two years previously and 'recently diagnosed' if it had been made within two years.

At most visits a blood sample was taken by

venepuncture or finger prick for the measurement of glycated haemoglobin A₁ (HbA_{1c}), fructosamine (glycated serum proteins), and blood glucose concentrations. The term 'glycated' is used throughout in preference to the more familiar 'glycosylated' because of the non-enzymic nature of the reaction. HbA_{1c} was measured by a microcolumn technique with m-phenyl-boronate agarose after incubation overnight to remove the unstable fraction.⁵ In this laboratory the assay has a coefficient of variation of 4% if HbA_{1c} is 12%, and 8% if HbA_{1c} is 5%. The method was not changed during the study. The laboratory is a founder member of the national quality control scheme for HbA_{1c} measurement of concentrations. This has shown no appreciable longitudinal alteration in results and the quality control performance has always been less than one SD of the mean for the method.⁶ The normal range for HbA_{1c} concentration is 5–9% (B Cockrill, personal communication), and 10% was the limit below which diabetic patients were considered well controlled. The results of the fructosamine estimations are being published separately.

To compare the efficacy of different insulin regimens 'soluble insulin' comprised Actrapid MC and Human Actrapid (Novo), Velosulin and Human Velosulin (Nordisk), and Humulin S (Lilly), 'isophane insulin' comprised Human Protaphane (Novo), Insulatard and Human Insulatard (Nordisk), and Humulin I (Lilly); and 'zinc insulin' comprised Monotard MC and Human Monotard (Novo), and Humulin Zn (Lilly). By the end of the three years most patients were controlled on human insulins manufactured by recombinant DNA methods.

All patients were taught to monitor blood glucose concentrations at home and given an Autolet (Ames) device with which to prick a finger to obtain a blood sample. Blood sugar was measured by either Visidex II (Ames) or B-M test 1–44 (Boehringer). Monitoring blood glucose concentrations at home was only introduced during the first year of the clinic; all but five patients accepted that it was the best way to monitor their day to day control.

Apart from one period of six weeks during the third year of the study patients were seen regularly by the author every three months and more frequently if problems arose. A dietitian was available to give advice but did not see all patients routinely. Two district nurses who had been trained by the home care team at Birmingham Children's Hospital were available to help manage patients at home, but in practice little expert nursing support or supervision outside the clinic was available. Most of the education of established diabetics was done in the clinic, and that of newly diagnosed patients in

hospital. Following discharge from hospital the patients were seen frequently (weekly at first) until it was felt that they and their parents were able to cope for longer periods between visits. The author could be contacted by telephone most of the time and steps were taken to ensure that all patients had access to a telephone. Dietary advice was given according to current British Diabetic Association recommendations and total intakes of calories were adjusted to try and maintain an ideal body weight for height. Parents were instructed to alter their child's insulin dose in order to prevent appreciable hypoglycaemia or recurrent hyperglycaemia.

A record of type of insulin dosage, frequency of administration, and calculated dosage related to body weight was made and entered into flow sheets together with height, weight, and HbA_{1c} and blood glucose concentrations.

Assessment of obesity was made using the formula:

$$(\text{actual body weight/actual body height}) \times (50\text{th centile height for age}/50\text{th centile weight for age}) \times 100.^7$$

This formula overestimates obesity in tall children of appropriate weight but enables valid longitudinal assessment of obesity to be made. A value of greater than 120% indicated clinically important obesity. Three children who were also being treated for hypothyroidism were excluded from consideration of the effect of the increased dose of insulin on body weight.

HbA_{1c} measurements were made for all patients at their first visit to the clinic between April and June 1983. To avoid the effect of seasonal variations in HbA_{1c} concentrations,⁸ results of measurements made during the three months April to June were used for comparison each year. If more than one value was available from this period each year the nearest to the anniversary of admission to the clinic was used in the statistical calculations. It was only necessary to make a choice in 29 (12%) instances. Other measurements were made at the same time.

The clinic population was studied in two groups. Most of the observations reported here refer to the results obtained from the entire group attending the clinic (group 1). Comparisons were also made between the following subgroups: male and female, prepubertal and postpubertal, established and recently diagnosed diabetics, those taking soluble and isophane insulins twice a day and those taking soluble and zinc insulins twice a day, and those whose HbA_{1c} concentrations were less than or greater than 10%. To eliminate any spurious effect on improvement in control caused by the addition of new patients to the clinic, changes in HbA_{1c} concentrations were studied in a second group

(group 2) which comprised only those patients who attended the clinic from its inception, were still attending three years later, and for whom four sets of data were available. The effect of increasing the dose of insulin on obesity was studied in these children at entry and after three years. Numerical values are expressed as mean (SD), and statistical comparisons were made by the Mann-Whitney U test, the Wilcoxon rank sum test, and the χ^2 test with Yates' correction as appropriate.

Results

Table 1 gives details of patients in each subgroup of group 1 during each of the time periods studied together with their ages, insulin dosage, and HbA_{1c} concentrations. There were consistently about 20% more boys than girls in the clinic. Fifty-two patients were admitted initially, and during the first year five new cases were diagnosed and one was transferred to the adult clinic. In the second year there were 16 new patients and two were transferred, and in the third year there were 10 patients and 10 were transferred. Thus for the last two years the clinic comprised 70 patients. Group 2 comprised 38 of these (21 boys and 17 girls). A total of 83 patients were seen in the clinic during the three years.

During the three years the mean age rose by one year from 12.1 (3.0) years; and the proportion of postpubertal children increased from 15 (25%) to 24

(34%). The group included one girl with Down's syndrome who was 20 years old and still prepubertal, but she subsequently began menstruating; she has remained in the clinic.

The proportion of newly diagnosed patients rose from 5 (9%) to 17 (24%) and of those taking more than one injection a day from 17 (33%) to 64 (91%). Of the latter all but two were having two injections a day except two who were having four, three of Human Actrapid through a Novopen and one of Human Ultratard through a conventional insulin syringe. There was also a 31% increase in the mean insulin dosage from 0.89 (0.29) U/kg/day in 1983 to 1.17 (0.35) U/kg/day in 1986 ($p < 0.001$).

Details of individual HbA_{1c} concentrations are shown in the figure. The mean initial HbA_{1c} concentration was 15.8 (4.7)% in the group as a whole and was higher in the girls than boys. Only one girl had a value of less than 10%. During the next three years the mean HbA_{1c} concentration for the group fell significantly to 9.9 (2.5)% ($p < 0.0001$) and was not significantly different between boys and girls, although over the three years the improvement occurred earlier in the girls than in the boys. By the end of the study 25 (65%) of the boys and 16 (52%) of the girls had concentrations of HbA_{1c} $< 10\%$.

When the data on duration of diabetes were analysed HbA_{1c} concentrations did not seem to be higher in those patients with longstanding diabetes. This may have been because of the relatively small

Table 1 Details of patients in group 1

	1983			1986		
	Total No	Boys	Girls	Total No	Boys	Girls
Age in decimal years						
Mean (SD)	12.09 (2.97)	12.9 (2.80)	12.10 (3.24)	13.08 (3.32)	13.36 (2.94)	12.72 (3.77)
Range	3.36-20.23	3.36-15.38	6.06-20.23	2.57-23.10	6.33-18.13	2.57-23.10
No prepubertal	39	23	16	46	28	18
No (%) postpubertal	13 (25)	6 (21)	7 (30)	23 (34)	11 (28)	13 (42)
No recently diagnosed	9	3	6	24	12	12
No (%) with established diabetes	43 (83)	26 (90)	17 (74)	46 (66)	27 (69)	19 (61)
No receiving one dose of insulin daily	35	19	16	6	5	1
No (%) receiving two or more doses of insulin daily	17 (33)	10 (34)	7 (30)	64 (91)	34 (87)	30 (97)
Insulin dosage in U/kg/day:						
Mean (SD)	0.89 (0.29)	0.92 (0.27)	0.83 (0.31)	1.17 (0.35)†	1.14 (0.35)†	1.22 (0.34)
Range	0.34-1.80	0.34-1.80	0.44-1.36	1.74-1.84	0.27-2.18	1.74-1.84
% Concentration of HbA _{1c} :						
Mean (SD)	15.8 (4.7)*	15.1 (4.2)*	16.6 (5.2)	9.9 (2.6)†	9.9 (2.6)†	9.9 (2.5)
Range	6.4-27.8	10.3-21.9	8.4-27.8	5.3-17.9	6.5-17.9	5.3-15.9
No (%) with % concentration of HbA _{1c} $< 10\%$	1 (2)*	0*	1 (4)	40 (59)†	24 (65)†	16 (52)
No with % concentration of HbA _{1c} $> 10\%$	51	28	22	28	13	15

*One value not available; †two values not available

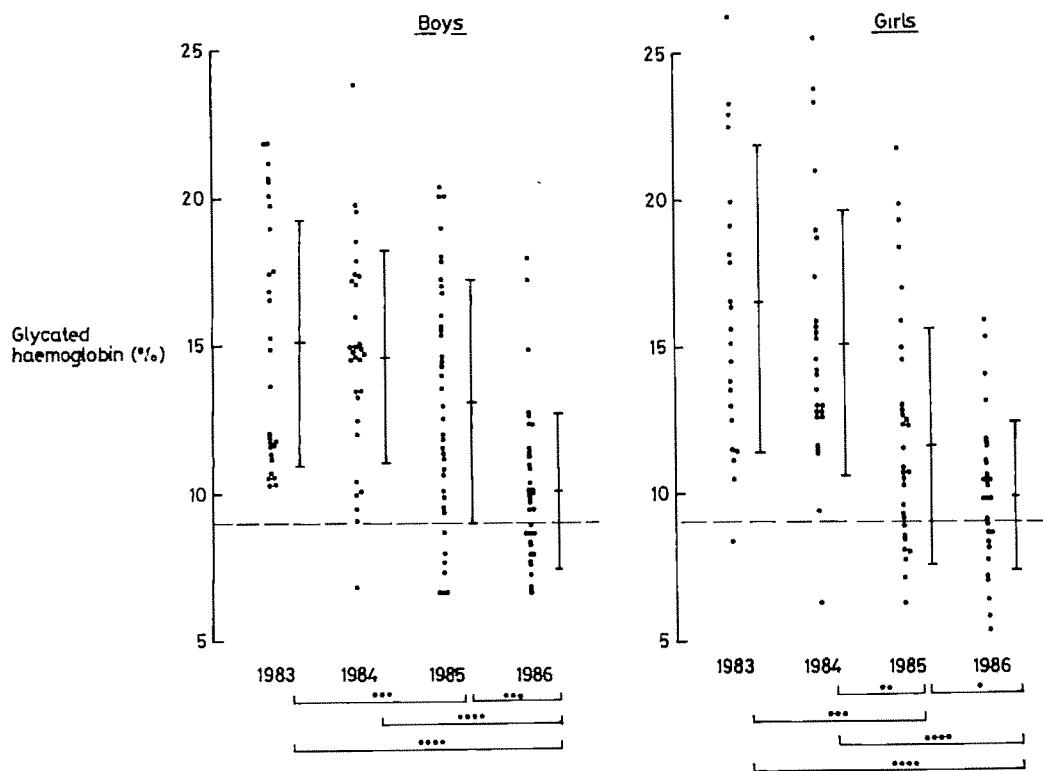


Figure Individual values of HbA_{1c} for boys and girls, 1983–1986. Each point is a single value from one patient taken between April and June. Vertical bars mean (SD), interrupted line = upper limit of HbA_{1c} in normal subjects. *= $p<0.05$, **= $p<0.02$, ***= $p<0.0005$, ****= $p<0.0001$

numbers. Recently diagnosed children, however (those who had had diabetes for less than two years), were satisfactorily controlled (HbA_{1c} concentration $<10\%$) consistently more often than established diabetics; this difference was significant ($p<0.001$) in 1985.

Prepubertal children were easier to control than postpubertal children, and this difference was largely due to differences between prepubertal and postpubertal boys. Prepubertal boys had consistently lower HbA_{1c} concentrations despite being on lower doses of insulin, there being a significant difference in either or both in all four years. This was true irrespective of whether or not recently diagnosed patients were included.

When the association between the mean insulin dosage of those children taking a combination of soluble and isophane insulin was compared with that of those taking soluble and zinc insulin, data were included only if the children had been diabetic for at least two years and were taking insulin twice a day. At all four time periods the mean HbA_{1c} concentra-

tions and the mean insulin doses were lower among those children taking soluble and isophane insulin than among those taking soluble and zinc insulin. There were significant differences between the two groups in mean HbA_{1c} concentrations in 1984 and 1986 and in mean insulin doses in 1983. When the results for the whole period were combined the difference between mean HbA_{1c} concentrations was highly significant ($p<0.001$) and the difference in insulin doses was not significant.

Details of the 38 patients who remained in the clinic throughout the three years of the study (group 2) are shown in table 2. The mean ages of the 21 boys and 17 girls were 11.6 (2.0) and 11.1 (3.1), respectively, and the mean duration of their diabetes 5.2 (3.4) years and 3.4 (2.9) years, respectively. None of the boys and only two of the girls were pubertal. By the end of the study eight boys and eight girls were pubertal. The mean HbA_{1c} concentration declined only slightly less than in group 1 during the three years. Within this group the index of obesity rose slightly from 100 (15)% to

Table 2 *Details of patients in group 2 (n=38)*

	1983			1986		
	Total No	Boys	Girls	Total No	Boys	Girls
% Concentration of HbA _{1c} :						
Mean (SD)	15.0 (4.5)	14.3 (3.9)	15 (5.2)	10.6 (2.7)	10.6 (2.9)	10.6 (2.4)
Range	8.4-27.8	10.3-21.9	8.4-27.8	6.4-17.9	7.4-17.9	6.4-15.9
Insulin dosage in U/kg/day						
Mean (SD)	0.86 (0.26)	0.90 (0.23)	0.8 (0.29)	1.28 (0.29)	1.29 (0.29)	1.30 (0.31)
Range	0.34-1.38	0.34-1.30	0.4-1.19	0.74-2.18	0.82-2.18	1.74-1.81

Table 3 *Duration of complications*

Complication		Duration of diabetes (years)
Retinopathy	1 (+1)	5.2
Nephropathy	3	3.0, 8.5, 12.4
Cataract	3	8.0, 12.4, 6.3
Necrobiosis lipoidica	1	0
Inflammation at site of injection	2	—

105.5 (10.6)% in the girls, and from 97.5 (10.3)% to 99.1 (12.4)% in the boys. None of these differences was significant. The increase among the girls is mainly accounted for by the substantial increases in body weight of the three whose indices were less than 50% on admission to the clinic.

The diabetic complications are summarised in table 3. Ten complications occurred in eight patients. Two patients developed inflammation of the skin at the site of injection. One patient had necrobiosis lipoidica which had been present at the time of diagnosis, and three had cataracts, one of which required removal. Three patients had histological evidence of diabetic nephropathy, and two of these also had cataracts. One patient had early retinopathy. In addition one of the patients with diabetic nephropathy may also have had retinopathy, but this could not be confirmed on routine examination because of her cataract.

Discussion

East Birmingham Hospital is a large district general hospital serving an urban population of just over 200 000. About a quarter are less than 16 years old and about a quarter are from Pakistan and Bangladesh. It also serves diabetic children from the neighbouring district of Solihull which has a population of just under 200 000. Recent figures suggest that the prevalence of diabetes in children under 10 years old is about 1.3:1000.^{9,10} A population of 400 000, in which a quarter are under the age of 16

would therefore be expected to yield about 130 cases of diabetes and the size of the clinic is less than this. Nevertheless, it represents a fairly typical urban diabetic population.

Glycated haemoglobin has become established as the standard measurement of intermediate term control of diabetes and it reflects glycaemic control over the preceding four to six weeks. It is now clear, however, that there is a considerable seasonal variation in HbA_{1c} concentrations with a nadir in spring and early summer.⁸ It is therefore important to measure and compare HbA_{1c} concentrations taken at the same time each year to make valid comparisons from one year to the next. Because care was taken to do this the effect of seasonal variation was eliminated.

Concern about the need for good control has led to the establishment of special clinics for diabetic children during the past decade, and control has been improved.¹¹ There is little information, however, about the results of establishing new clinics for diabetic children, or about the quality of control achieved by children not attending such clinics. The establishment of a children's diabetic clinic here has resulted in a considerable improvement in control as measured by the fall in mean HbA_{1c} concentrations.

Three aspects of the insulin dosages and regimens were associated with the improvement. Total mean insulin dosage increased and was accompanied by a substantial rise in the proportion of patients taking insulin twice a day and by a change to a combination of soluble and isophane insulin rather than soluble and zinc insulin. The mixture of soluble and isophane insulin seemed to be more effective in maintaining good control, and hypoglycaemia and obesity were not major problems. Furthermore, newly diagnosed and prepubertal children seemed to be easier to control than established or post-pubertal diabetics. The former is likely to be due to persisting residual insulin secretion. The reasons for the latter observation, which is not new,¹¹ can only be speculated upon but may help to explain part of the increase in insulin. The improvement in mean HbA_{1c} concentrations, however, cannot be attri-

buted to the inclusion of newly diagnosed as well as established diabetics because the progress of patients in group 2 was nearly as good as that in the whole clinic.

It should be noted, however, that most of these observations were made retrospectively and the treatment groups were not adequately controlled to provide a sound basis for guidelines for insulin treatment. Nevertheless the observations are potentially valuable and may be confirmed by further work.

The introduction of the system of monitoring blood glucose concentrations at home may have been a factor in recognising the need to increase insulin dosages in some cases and it is worth noting that little improvement occurred during the first year before the system was introduced. Though it is a necessary part of assessing overall glycaemia and fluctuations in blood glucose,¹² monitoring blood glucose concentrations at home may only play a small part in maintaining control, and attention to other details is probably more important.¹³

Perhaps the most worrying aspect of this study is that ten complications occurred in eight of the 83 patients. The two instances of inflammation of the injection sites were probably caused by poor hygiene and they did not have any long term detrimental effects. The patient with necrobiosis lipoidica already had lesions at the time of diagnosis. There were, however, seven long term serious complications in five other patients. If it is accepted that improved control leads to a delay in the onset of serious complications,¹⁴⁻¹⁷ then it can only be concluded that the establishment of a paediatric diabetic clinic has led to a better prognosis for our patients.

Though the establishment of the clinic has led to an improvement in control and brought to light a few children with serious complications, it has also led to a number of benefits which are difficult to quantify and impossible to subject to statistical analysis. Many parents expressed their appreciation of seeing the same person at each visit to the clinic and of receiving advice that was consistent from one visit to another. This is particularly important in the education of new diabetics in whom it is important to establish good habits and set high standards of control from the outset so that the risk of complications is reduced to a minimum.

This study has shown that a paediatric diabetic clinic in a district general hospital can confer considerable benefits. The results provide further evidence to support the recommendation of the British Paediatric Association that 'clinics for diabetic children be established in each district

general hospital . . . There should be at least one paediatrician in each district with a special interest in diabetes' (British Paediatric Association Autumn Newsletter, 1986)

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Evaluation of infants by echo planar imaging after repair of diaphragmatic hernia

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SUMMARY Three infants were studied by echo planar imaging after repair of congenital diaphragmatic hernias. Total lung volume and individual lung volumes were estimated using echo planar imaging. In the two patients with left sided hernias, the right lung was more than twice as large as the left. The patient with a right sided hernia had developed emphysema on the right side, and the right lung was twice as large as the left when estimated by echo planar imaging. Echo planar imaging studies took less than five minutes to perform and no sedation was required.

Echo planar imaging is a form of magnetic resonance imaging that gives short image acquisition times and that permits a sequence of images to be rapidly obtained. Each image is displayed in transection as it is acquired in real time. Images may be constructed from the data in the sagittal, coronal, or any other plane, and transformed into a film sequence if required.

We have used this technique to investigate three infants after repair of congenital diaphragmatic hernias. Necropsy studies of children with such hernias have shown pronounced hypoplasia of both lungs in those that died soon after birth.¹ Plethysmographic studies show that most babies achieve normal lung volumes in the first weeks of life after successful repair of diaphragmatic hernias.² The accuracy of the plethysmographic method of estimation of lung volumes in infants has recently been questioned, however.³ Because echo planar imaging is not invasive and requires no sedation, the possibility of measuring individual and total lung volumes is practical and we present preliminary measurements.

Patients and methods

The principles of nuclear magnetic resonance imaging of discrete structures were first introduced by Mansfield and Grønneil in 1973.⁴ Echo planar imaging is an extension of these principles and the details of its development and use in medicine have been reported elsewhere.⁵⁻⁷

Echo planar imaging requires no gating because each image is a snapshot acquired in 64 milliseconds. Each image is therefore comparatively free of motional artefact caused by either cardiac or respiratory movement. It follows that echo planar imaging may be useful in infants who have high heart and respiratory rates.

Each transectional image is 7 mm thick and comprises an original image array of 64×64 pixels that correspond to a true in plane resolution of 3 mm. For display and photographic purposes the array is linearly interpolated up to 256×256 points. Consecutive images may be acquired prospectively by gating during consecutive cardiac cycles with the first image of each sequence triggered from the QRS complex. An alternative triggering mode uses a fixed delay from the R wave peak. This effectively freezes heart motion at a particular point in the cardiac cycle, but permits movement of the thorax to be seen in a film sequence. Film sequences may also be constructed of each slice showing patterns of blood flow. Blood at a standstill gives a relatively high signal and looks bright. Blood moving out of the imaging plane of the study yields little signal and looks black.

Additionally, constructions in the sagittal, coronal, or any other plane may be made and transformed into a film sequence. Each study of the thorax took less than five minutes and no sedation was required.

The initial transectional image was obtained starting at the apex of the lung and continuing in

6 mm steps towards the base until lung could no longer be seen. The area of the lung at each stage was measured by planimetry and multiplied by the stage thickness to give total and individual estimates of lung volumes. Each of the transectional images comprised an average of 16 snapshots taken in rapid succession over a 10 second period. Thus the lung volumes calculated tend to reflect the volume in the middle of a tidal breath.

Case reports

CASE 1

A 9 month old baby boy had been born at 38 weeks' gestation by caesarean section after an uneventful pregnancy. He had made no attempt to breathe and required intubation and ventilation. A right sided diaphragmatic hernia was diagnosed on chest x ray picture. Surgical repair was performed at 14 hours of age. The size of the defect necessitated the insertion of Xenoderm patches on the diaphragm and on the musculature of the abdominal wall. The skin was closed normally. The infant was ventilated for 23 days and required supplementary oxygen for 28 days. Tolazoline and dopamine infusions were given for six days and maximum ventilatory requirements were pressure 30/3, rate 90/minute in 100% oxygen.

Echocardiography showed that the heart was normal. After discharge his parents noted that he often became wheezy, and the wheeze was severe

when associated with upper respiratory tract infections. On examination he was gaining weight along the third centile, developing normally, and had pectus excavatum and decreased air entry over the right lower lobe.

Radiological investigation showed intermittent shadowing of the right upper lobe and the most recent films show the right hemithorax to be almost filled by aerated middle and lower lobe. The bronchus of the right upper lobe arose at the carina (fig 1). Barium meal examination showed oesophageal reflux and a sliding hiatal hernia.

Figure 2 shows four echo planar imaging transections corresponding to planes 12, 14, 17, and 18 taken from a set of 18 contiguous slices starting at the apex of the lung. Figures 2(A) and (B) show the pectus deformity, over expansion of the lower zone of the right lung, and displacement of the heart into the left side of the thorax. Figures 2(C) and (D) show the Xenoderm patch. When lung volumes were estimated by our method, the right lung was 2.03 times as large as the left, and the total lung volume was 28 ml/kg (the baby's weight at the time of the study was 8000 g).

CASE 2

A 10 week old baby girl had been born at 37 weeks'



Fig 1 Chest x ray picture of case 1 at the time of echo planar imaging. Note collapse of right upper lobe, deviation of trachea to right, and hyperinflation of right middle and lower lobes.

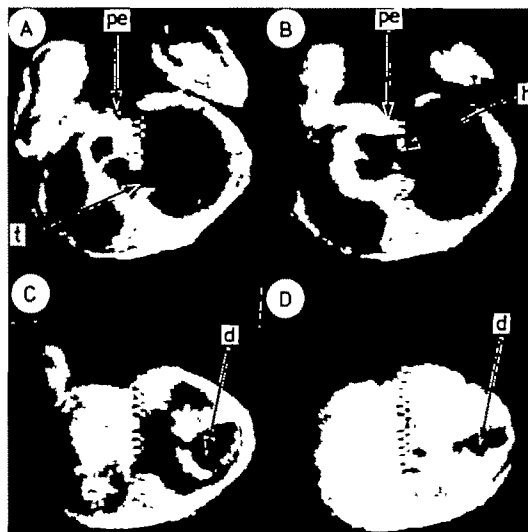


Fig 2 Transectional echo planar images through the thorax of case 1. (A) and (B) show sections through mediastinum at mid-systole with heart mass and chambers (h). Trachea (t) is also visible in (A) as a bright ring structure posterior and right of heart. Note pectus excavatum deformity (pe) and hyperinflation of right lung. Diaphragmatic repair patch (d) is seen in (C) and (D).

Table Total and individual lung volume in three infants with diaphragmatic hernias

Case No	Side of hernia	Estimation of lung volumes		
		Left lung (ml)	Right lung (ml)	Total lung volume (ml/kg)
1	Right	71	149	28
2	Left	23.4	51.8	25
3	Left	62	110	43

gestation. Resuscitation, including ventilation, paralysis with pancuronium, infusion of dopamine, and drainage of a right sided pneumothorax had been required before operative repair of her diaphragmatic hernia when 12 hours old.

A large left posterior lateral defect had been found in the diaphragm with the stomach, spleen, left lobe of liver, and some small and large bowel in the chest.

Postoperatively she required ventilation with maximum pressures of 24/4, rate 60/minute, and oxygen of 100%. Dopamine and tolazoline were given for seven days. After discharge from hospital at 20 days of age she remained symptomless.

When lung volumes were estimated by our method, the right lung was 2.04 times larger than the left, and the total lung volume was 25 ml/kg (the baby's weight at the time of the study was 3000 g).

CASE 3

An 8 week old baby boy had been born at term and had required resuscitation at birth before being operated on at 7 hours of age. His left diaphragmatic hernia was closed easily and the volume of the left lung was reported as 'good' in the postoperative notes. Ventilation was required for six days and tolazoline and dopamine were given for five days. Maximum pressure was 20/4, rate 50/minute, and inspired oxygen 90%. He remained symptomless after discharge from hospital.

When lung volumes were estimated by our method, the right lung was 1.7 times larger than the left, and the total lung volume was 43 ml/kg. Estimated lung volumes are shown in the table.

Discussion

Magnetic resonance imaging is free of hazards, and the studies of the chests of these infants by echo planar imaging were completed within five minutes with no need for sedation.³

We have described a new method of calculating total and individual lung volumes in infants who

have had diaphragmatic hernias repaired. Studies in which measurements were made by total body plethysmography have shown that after successful surgical repair of diaphragmatic hernias most babies achieve normal lung volumes in the first weeks of life.² Some infants had reduced lung volumes that tended to become normal later in the first year of life, and a small number were hyperinflated.

Plethysmographic studies in infancy require sedation, and because of the doubtful accuracy of estimates of thoracic gas volume in this age group, especially in infants with obstructed airways,³ lung volume estimation by echo planar imaging will be clinically useful. Thoracic gas volume is an indication of aerated lung volume, and a measurement of total lung capacity would be a more accurate indication of the degree of lung hypoplasia.

The two patients with left sided hernias had right lungs that were twice as large as the left, suggesting decreased growth on the left. The total lung volume of 25 ml/kg measured by echo planar imaging in the second patient was small for her age when compared with published estimates of thoracic gas volume in normal infants (30–35 ml/kg). The difference would be even greater if tissue volume—which is included in estimation by echo planar imaging—were subtracted, and this might indicate hypoplasia of her lungs. Not all the dead space is measured by echo planar imaging but this is assumed to be comparatively small. Interestingly, the third patient, who was thought at operation to have a lung of good size on the side of the hernia, had a total lung volume of 43 ml/kg (table).

The first patient had radiological evidence of hyperexpansion of his right middle and lower lobes nine months after repair of his right diaphragmatic hernia. Measurement of individual lung volumes support this, his right lung being more than twice as large as his left.

There is pathological evidence that there is pronounced hypoplasia of both lungs in infants who die soon after birth with congenital diaphragmatic hernias.¹ As suggested by Landau *et al.*,² however, and by radiological evidence, the ipsilateral lung may appear to fill the whole hemithorax within one week of operation,⁹ and gross hypoplasia does not always persist throughout infancy.

Using the techniques of intensive care developed over the past 10 years, a larger number of babies with pronounced hypoplasia of the lungs now survive. It will be interesting to follow the individual growth of their lungs.

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Dry lung syndrome after oligohydramnios

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SUMMARY We studied four infants whose mothers had had leaks of amniotic fluid for varying periods before birth. Three were associated with compression deformities. Oxygenation was achieved only by overriding the pressure limit safety devices on the resuscitation apparatus and ventilating after birth with high inflation pressures. In all cases the ventilation pressures had to be further increased for 12 hours but rapid improvement followed on the second day so that all four were spontaneously breathing air after a few days. It is postulated that collapse of the airways resulted from oligohydramnios, and that the resulting 'dry lungs' would only respond to high inflation pressures.

It seems that adequate quantities of amniotic fluid are required for the satisfactory development of the fetal lung.^{1,2} Oligohydramnios associated with renal agenesis or gross dysplasia is well recognised as a cause of pulmonary hypoplasia that is so severe that the infants die very shortly after birth.^{3,4} More recently the association between pulmonary hypoplasia and prolonged leakage of liquor following both spontaneous membrane rupture and amniocentesis has been described, again usually with fatal outcome.^{5,6}

We report the association between severe early respiratory distress in four babies after prolonged leak of amniotic fluid in whom the respiratory distress improved remarkably on the second or third postnatal day. We postulate that this was due to secondary reduction in the lung fluid and effective lung volume (dry lungs) due to the external compression and the leak of fluid. Physical distension of the lung by higher pressures than normal may allow survival.

Patients

Of 115 premature babies of less than 37 weeks' gestation with premature and prolonged rupture of membranes (longer than 99 hours) who were managed in the neonatal unit at this hospital between January 1980 and January 1987, 11 died shortly after birth from respiratory insufficiency associated with hypoplastic lungs, six confirmed at necropsy. In many cases extremely high inflation pressures had been required to achieve oxygenation at the resuscitation, and further increases in ventilator pressures had been necessary during life before the almost

invariable development of air leaks. In many cases hypoxia occurred gradually when it was impossible to provide higher airway pressures on the ventilators (Bournes BP200 or Sechrist). All the babies who died had skeletal deformities consistent with oligohydramnios tetrad.²

In four infants a similar early course was seen, but on the second or third days of life, after we had used extremely high peak inflation pressures, a sudden and dramatic improvement occurred and the infants rapidly ceased to require ventilatory assistance or supplementary oxygen. These four cases are described below. During the period of this study no infants were seen with a similar clinical story in whom the membranes had been ruptured for less than 99 hours.

CASE 1

Mrs D had premature rupture of fetal membranes at 31 weeks' gestation. She was treated with ritodrine, betamethasone, and amoxycillin and continued to leak large volumes of liquor until delivery eight days later. The baby's heart rate at delivery was 50, but despite intubation and intermittent positive pressure ventilation that led to a prompt increase in the heart rate, the infant remained blue. There was poor air entry (worse on the left) and although the infant began spontaneous respiration he remained blue. There was a fixed flexion deformity at the left elbow and deformed feet. In view of the persistent cyanosis and the poor chest movements a diagnosis of diaphragmatic hernia was considered, but the chest radiograph showed only airless lungs compatible with congenital pneumonia. After two hours in 100% oxygen the baby became pink but carbon

dioxide retention continued for 12 hours. He was then extubated, and did not require supplementary oxygen after 21 hours. No pathogens were grown from the sputum and he made an uncomplicated recovery.

CASE 2

Mrs K had an amniocentesis at 16 weeks because a previous infant had had a neural tube disorder and she had a high plasma concentration of α fetoprotein. She had a continuous leak of amniotic fluid following this procedure, and oligohydramnios was diagnosed on ultrasonography. A caesarian section was performed electively at 33 weeks' gestation. At birth the baby's heart rate was unrecordable and there was no respiratory effort. The heart rate improved after intubation and intermittent positive pressure ventilation, but the baby remained blue with poor air entry. The baby was reintubated three times because of apnoea and bradycardia, and only became pink when the pressure release button on the resuscitation apparatus was overridden. Continuous inflation with a bag compressed by hand at high pressure finally achieved oxygenation. On transfer to the special care baby unit the chest radiograph showed small, airless, 'hypoplastic lungs'. There were Potter's facies and many limb deformities including bilateral genu recurvatum. The baby was stabilised on extremely high mean airway pressure of 22 cm H₂O and 100% oxygen but over the next 24 hours it was possible to reduce these to 12 cm H₂O and 30% oxygen. At 48 hours the baby was transferred to continuous positive airway pressure and at 60 hours she was extubated and breathing air. No pathogens were grown from the sputum, the respiratory rate was normal by 10 days of age, and she made an uncomplicated recovery.

CASE 3

A baby girl was born at 27 weeks' gestation by caesarean section for breech preterm labour 23 days after the spontaneous rupture of fetal membranes. Oligohydramnios was confirmed by ultrasonography. There was no spontaneous respiratory effort at birth and the Apgar score was 3 at one minute, so she was intubated and given intermittent positive pressure ventilation. Because of bradycardia, cyanosis, and poor chest movements with the pressures normally used for resuscitation, the pressure release valve on the resuscitation bag was overridden and the infant was transferred to the neonatal unit where high inflation pressures were used. There were pronounced contraction deformities of all four limbs. During the next five hours

because of persistent cyanosis despite being given 80–100% oxygen, the peak airway pressures were gradually increased to a maximum of 32 with an end pressure of 6 cm H₂O (a mean airway pressure of 19). The chest radiograph showed airless lungs compatible with surfactant deficiency or severe bilateral congenital pneumonia. Using a variety of conventional ventilator rates (20 to 60) she had persistent dusky spells on 100% oxygen and inflation with a bag compressed by hand was required. Precarious oxygenation was eventually achieved using a peak airway pressure of 32, an end pressure of 4, a 1:1 inspiratory ratio, and a ventilator rate of 140/minute. The mean airway pressure was 18 or more because of probable inadvertent end pressure at this ventilator frequency. Tolazoline was given without notable improvement in oxygenation. Frequent inflation with a bag compressed by hand at high pressure was required during the first 12 hours. After 16 hours the infant was stabilised on a peak airway pressure of 26, end pressure of 7, ratio of 1:1, a ventilator rate of 35/minute, and a mean airway pressure of 16.5. By 24 hours of age the mean airway pressure had been reduced to 10 and the oxygen to 75%. There was then steady and rapid improvement until she was extubated on the fourth day of life, and she was spontaneously breathing air on the fifth day. No pathogens were cultured from the secretions at any stage in the illness. Over the five weeks until discharge from hospital she had a respiratory rate which was on occasions over 60/minute at rest, but at follow up at 4 months old there were no chest problems or signs.

CASE 4

Mrs L had several small antepartum haemorrhages after 21 weeks' gestation. At 27 weeks a further haemorrhage was followed by a pink watery loss. Ultrasound examination after this showed 'no liquor' and examination using a speculum confirmed the loss of blood stained amniotic fluid. She continued to leak fluid freely over the next 10 days when a further ultrasound examination showed a liquor column of only 1 cm. Amniocentesis showed a lecithin:sphingomyelin ratio of 2:2 in the liquor, so at 28 weeks and six days a caesarean section was performed. Intermittent positive pressure ventilation and 100% oxygen were required to resuscitate the baby girl. No contractural deformities were apparent. By 8 hours of age a mean airway pressure of 14 cm H₂O and 90% oxygen were required to achieve oxygenation. The chest radiograph at six hours showed a 'white out' compatible with severe surfactant deficiency or bilateral congenital pneumonia. Over the next six hours, however, it was possible to reduce the oxygen to 35%. A repeat

chest radiograph taken at 18 hours of age showed complete aeration and no obvious disease. Forty-eight hours later ventilatory support was withdrawn and on the fifth day she was breathing spontaneously on 25% oxygen. She had a pronounced tachypnoea and needed 25% to 35% oxygen in the incubator for the two months, repeated chest radiographs showing slight haziness bilaterally but no definite evidence of consolidation or infection. Since discharge she has been admitted several times with wheeziness and even when her chest sounds clear there is some recession.

Discussion

The diagnosis of anatomical pulmonary hypoplasia during life depends on the clinical finding of oligohydramnios, a low Apgar score, the presence of deformities, and an unusual postnatal pulmonary course.⁵ This resembles severe respiratory distress syndrome with persistent pulmonary hypertension, but differs in that there is immediate onset of severe pulmonary insufficiency requiring high ventilator pressures.⁶ Chest radiographs are variable, in some infants showing airless lungs compatible with the respiratory distress syndrome, in some small clear lung fields and in some compression deformity of the thorax so that it is bell shaped.⁷

In three of the infants reported here the association between positional deformities of the limbs and prolonged leakage of liquor amni made it reasonable to assume that their respiratory problem was pulmonary hypoplasia. Despite the absence of postural deformity, the fourth patient had severe oligohydramnios shown on ultrasonography during the 13 days before delivery. Hypoplasia of the lungs seemed to be confirmed in the delivery room in each case by the need to override the pressure control on the resuscitation apparatus to achieve oxygenation. Once the infants had reached the neonatal unit and the compression deformities and Potter's facies were evident we decided to use high mean airway pressures to ventilate them. In all cases antibiotics were given in case they had congenital pneumonia, but no bacteriological confirmation was ever obtained. The fourth case, despite the absence of positional deformities, seems to have had pulmonary hypoplasia similar to that described by Perlman *et al.*⁸

In all cases the ventilation pressures had to be increased further in the first 12 hours of life to achieve adequate oxygenation. It was difficult then to know whether additional surfactant deficiency was compounding the problems, particularly as the chest radiographs suggested little aeration. The high lecithin:sphingomyelin ratio in the fourth

infant, and the improvement in all the infants on the second day at a time when surfactant deficiency would be worsening, made this diagnosis unlikely. All the infants had low Apgar scores but we believe that this was largely because of our inability to expand the lungs at the resuscitation rather than because of pre-existing asphyxia.

It seems possible that a temporary 'functional hypoplasia' was the cause of this clinical condition where the lungs had leaked dry of the normal volumes of lung fluid and collapsed, necessitating high pressures to reopen them. This partial pulmonary hypoplasia has been alluded to before. Perlman *et al* described a case in which an infant had facial and limb deformities after a leak of liquor for 16 days together with a pulmonary condition which, though it did not require ventilation, was felt to be consistent with anatomically and functionally small lungs at birth with 'compensatory hyperplasia later'.⁸ In a group of 21 infants reported by Thibeault *et al* who required ventilation and who had positional deformities following prolonged leakage of liquor three survived; these may also have been instances of 'dry lung syndrome' but the details of the care and course are not given.⁶

Alcorn *et al*⁹ showed that although chronic drainage of liquor for three to four weeks in fetal sheep reduced the amount of lung tissue and its anatomical development, the biochemical maturation was enhanced leading to increased numbers of type 2 cells with lamellar material present both within the cells and within the alveolar lumen. Richardson *et al* showed that in the human fetus prolonged rupture of the fetal membranes led to acceleration of maturation of the fetal lung over a few days.¹⁰ Wigglesworth and Desai showed that the hypoplastic lungs associated with oligohydramnios had narrow airways and there was a failure of elastic tissue development round the airways and terminal sacs.¹¹ It is conceivable therefore that physical distention of the airways with high pressures over the first days of life might encourage comparatively mature biochemical mechanisms to promote satisfactory oxygenation. This seems a more reasonable explanation of the time course than the rapid hyperplasia of the lungs that was postulated by Perlman.⁸

Recently Blott *et al* described how pregnancies with oligohydramnios associated with rupture of the membranes during the second trimester have a satisfactory outcome if fetal breathing movements continue.¹² The presence or absence of fetal breathing movements is not recorded in our cases, but the duration of rupture was shorter, being 8, 13[?+42], and 23 days in the first three cases though not in the fourth (119 days). It seems

unlikely that the moment that fetal breathing stops the infant develops anatomical hypoplasia, but it might be that with the cessation of breathing movements the lungs collapse leading to temporary dry lungs due to unrestrained compression

With modern obstetric policies more mothers with early premature rupture of the membranes are being managed conservatively. It would seem appropriate not only to monitor the volume of liquor and the strength of fetal breathing movements obstetrically, but to deliver these infants electively with paediatricians in attendance who are of sufficient seniority to assess immediately whether the normally accepted inflation pressures may need to be overridden.

I thank junior staff able to intelligently and appropriately overrule policy. These infants would not have survived without them

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Short reports

Diphtheria—the continuing hazard

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SUMMARY An unimmunised schoolchild with no history of foreign travel developed severe diphtheria. Epidemiological investigations led to the discovery of a child in the same class with cutaneous diphtheria who had just returned from Bangladesh; this highlights the importance of swabbing all skin lesions acquired in endemic areas during any outbreak investigation.

In the United Kingdom today diphtheria is a rare disease. Notifications for the last decade have ranged from 0 to 5 each year, yet despite this apparent success the case fatality rate has increased from 4.6% for the years between 1940 and 1955 to 7.7% between 1955 and 1982.¹ One of the factors that may account for this is unfamiliarity with the disease leading to late diagnosis or misdiagnosis, which may have disastrous consequences.^{2,3} It is important to maintain a high level of clinical awareness of the disease. We describe the most recent case of diphtheria in Manchester and the steps taken to limit spread in the community.

Case report

In September 1985 a 6 year old unimmunised white boy presented to the paediatric department of a neighbouring hospital with a six day history of malaise, sore throat, and croupy cough. He had enlarged tonsils covered with white exudate and intermittent stridor. Streptococcal tonsillitis was diagnosed and treatment started with phenoxymethylpenicillin. The next day increasing stridor and spreading exudate led to a visit by one of us (BKM) and a diagnosis of diphtheria was made from the clinical signs. Emergency tracheostomy was performed on transfer to the Regional Infectious Diseases Unit (RIDU); this was followed by administration of 40 000 units of antitoxin and start of a 14 day course of erythromycin. Between the

third and the 14th day after admission, frequent atrial and ventricular extrasystoles, non-specific S-T changes, and runs of supraventricular tachycardia lasting 3-4 seconds were recorded. No neurological sequelae were detected and the child was discharged well 26 days after admission.

Epidemiological and bacteriological measures

The medical officer for environmental health was immediately informed of the clinical diagnosis, and outbreak control measures were instituted through close cooperation between his department, the RIDU, and the Manchester Public Health Laboratory. Nose and throat swabs from the patient were put into a commercial charcoal-containing transport medium (Probact, Technical Service Consultants, Bury) and plated on to Hoyle's tellurite medium within a few hours. The isolate from the child was a typical gravis culture shown to be toxigenic by a modification of the Elek test.⁴ The subsequent isolates from carriers were similarly identified.

The paediatric ward was immediately closed to admissions and discharges. Parents and staff were advised to stay at home until two sets of negative nose and throat swabs were obtained. No carriers were detected. In the patient's family, because of the father's distrust of vaccines, three other siblings were also unimmunised and they were given erythromycin prophylaxis and started on a primary immunising course for diphtheria and tetanus. No carriers or preclinical cases were detected.

Swabbing of the children at the infant school attended by the index case was started five days after presentation and was repeated twice at weekly intervals. Computer records showed that all the children had been adequately immunised against diphtheria. A search for any hidden case of cutaneous diphtheria in any child who had recently returned from the tropics led to the discovery of a 5 year old, fully immunised, British born Bangladeshi child in the same class as that of the index

case. This child had returned from Bangladesh three weeks earlier with multiple crusting lesions on his scalp from which a profuse growth of *Corynebacterium diphtheriae* var *gravis*, as well as *Staphylococcus aureus* and *Streptococcus pyogenes* was obtained. He was clinically regarded as a case of 'cutaneous diphtheria.' His scalp lesions healed rapidly on erythromycin.

Swabbing of the children at the infant school produced eight throat carriers among 132 pupils who shared common play areas and dining hall. Eight more throat carriers were discovered among contacts of these carriers. They were the mother, sister, and younger brother of the 'cutaneous diphtheria' case, two class mates of the sister who attended the local junior school, a younger pre-school sibling of one of these two children, and two household contacts of one of the carriers from the infant school. The carriers were treated with a 14 day course of erythromycin at the RIDU and discharged after three sets of negative nose and throat swabs. Three further sets of swabs were obtained before they were allowed to restart school or work. There were no cases of bacteriological relapse. In all, 21 people were admitted—16 carriers, one laryngeal and one cutaneous diphtheria case, and three others whose swabs subsequently proved negative. Around 800 people were screened; this generated a little over 3000 specimens.

Discussion

The isolation of toxigenic *C. diphtheriae* from a patient has important public health implications. The prevalence of such organisms in the United Kingdom is extremely low, so the spread in the community to and from a clinical case can be detected by swabbing of close contacts. Most toxigenic organisms are introduced from abroad and such sources should be looked for in every survey. Bangladeshi families have played an important part in the epidemiology of diphtheria in the United

Kingdom in the last 10 years.^{1 2 5} We consider the child with cutaneous diphtheria to be the source of the toxigenic organisms in this outbreak. Skin carriage of *C. diphtheriae* can be very persistent and is common in the tropics where it probably contributes towards natural immunity. Swabs taken from skin lesions acquired in endemic areas should be cultured for corynebacteria in addition to the more usual pathogens. Skin carriers are also more infectious than either nose or throat carriers.⁶ This outbreak also shows how toxigenic *C. diphtheriae* can spread rapidly even in immune populations. In the 20 days between the beginning of term and the first swabbing exercise the organism had spread to nine children in three different classes, into another school, and into households involving three or more people. The unimmunised cannot therefore rely on herd immunity for protection and the risk to such people can only increase as air traffic between the United Kingdom and endemic areas grows.

We would like to thank Dr Alan Davies, medical officer for environmental health, of Tameside District for his help and encouragement with this report

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Neonatal screening for cystic fibrosis

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SUMMARY Two groups of patients with cystic fibrosis were compared. The screened group, detected with an improved neonatal screening assay for immunoreactive trypsin, developed fewer chest infections requiring treatment and gained more weight than the unscreened group. Early diagnosis by screening seems to affect early morbidity.

Neonatal screening for cystic fibrosis by dried blood spot has been undertaken at several centres since the development of the serum immunoreactive trypsin (IRT) assay by Crossley *et al.* in 1979.¹ This test has been improved, notably by the human trypsinogen monoclonal antibody assay (HTMAB),² and it is effective and specific with acceptably few false positive and false negative results.^{3,4} Nevertheless, controversy exists as to whether the long term benefits⁵ of screening outweigh the economic and psychosocial costs.⁶

We report our experience with neonatal screening for this disease and compare the clinical progress during the first two years of life of a cohort of 28 patients with cystic fibrosis diagnosed by screening with a cohort of 23 patients who were clinically diagnosed. They were matched as closely as possible in terms of age and management.

Methods and results

Neonatal screening was introduced as a six month pilot study in two obstetric hospitals in Brisbane, Queensland in December 1982 (where 45% of Queensland births take place), and it was thereafter extended to all births throughout the state. Until December 1986 180 000 newborn babies were tested by the IRT assay method of Crossley *et al.*; the last 45 000 babies were also tested by the HTMAB assay. Since July 1982 99.5% of all newborn babies in Queensland have been tested. Table 1 shows the results and details of the programme. After a persistently raised IRT concentration diagnosis was confirmed at one month of age by at least three sweat tests (using p-bocarpine iontophoresis for sample collection). Patients were managed by a centralised and standardised management pro-

gramme for cystic fibrosis that was coordinated jointly from the two main paediatric teaching hospitals in the State of Queensland (Royal Children's Hospital and Mater Children's Hospital). During the study period no important changes in management protocol or philosophy of management occurred.

A comparison was made between two unselected cohorts of children with cystic fibrosis, who were born in Queensland between January 1980 and July 1985, with particular reference to illness during the first two years of life. The first cohort of 'unscreened' children (n=23) were born between January 1980 and July 1983 and were subsequently diagnosed clinically ranging from 0 months to 3.5 years (mean 0.6 years). The second cohort of 'screened' children (n=28) were born between December 1982 and July 1985. Patients presenting with meconium ileus were not included. Three (13%) patients in the unscreened group were (relatively) asymptomatic at diagnosis because they were diagnosed only after a sibling index case was found by screening. Clinical data concerning the first two years of life were collected retrospectively in both groups by a combination of data from the cystic fibrosis clinic medical record review, parent interview, and postal questionnaire. A comparison between the two groups is shown in table 2 and indicates items where a difference was found. No

Table 1 Details of the cystic fibrosis neonatal screening programme in Queensland

	Immunoreactive trypsin assay	Human trypsinogen monoclonal antibody assay
Total No screened	180 000	45 000
Re-sample rate	8/1000	4/1000
Rate at which children are referred for clinical evaluation	3.6/10 000	3.5/10 000
Predictive value positive at one month (probability affected)	0.85	0.9
False reassurance rate (cases missed)	0.23/10 000	—

Table 2 Comparison of closest possible match of patients with cystic fibrosis diagnosed during the screening programme with those diagnosed clinically with particular reference to morbidity in the first two years of life

	Screened (n=28)	Unscreened (n=23)	Result of statistical analysis
Male/Female ratio	1.5/1.0	1.3/1.0	
Age at diagnosis (in years) mean (range)	0.1 (0.02-0.12)	0.6 (0.03-2.3)	
Symptoms at diagnosis No (%) patients	3 (14)	21 (91)	p<0.001 Fisher's exact test
Average time from onset of symptoms to diagnosis (years)	—	0.5	
Medical consultations before confirmed diagnosis (No (%))			
None	26 (93)	2 (9)	
1-2	2 (7)	5 (22)	p<0.001
3-10	0	7 (30)	$\chi^2=3.77$
≥11	0	9 (39)	
Treated chest infection at 2 years of age (No (%))			
Up to 2	19 (68)	9 (39)	$\chi^2=5.56$
3-10	9 (32)	12 (52)	p<0.01 >0.05
≥11	0	2 (9)	p<0.025 Fisher's exact test
Hospital admissions at <2 years of age (No (%))*			
Up to 2	20 (72)*	16 (70)	
3-5	41 (14)	5 (22)	NS
6-10	4 (14)	2 (9)	$\chi^2=0.739$
Mean (SD) body weight (kg)			
Birth	3.2† (0.14)	3.1 (0.42) (n=22)	NS
6 months	7.0 (1.1)	6.3 (0.70) (n=15)	p<0.001 (Student's t test)
12 months	9.5 (1.28)	9.0 (1.15) (n=13)	NS
24 months	12.3‡ (1.35)	11.8 (1.59) (n=20)	

*All screened patients had an initial routine admission for assessment and education. All patients were managed concurrently by a co-ordinated cystic fibrosis clinic. Patients with meconium ileus were excluded from both groups.

†Twenty fifth percentile.

‡Fiftieth percentile.

differences were found in sex ratio, birth weight, or number of hospital admissions, but significant differences were observed in the age of diagnosis, time from onset of symptoms until diagnosis, the number of medical consultations before diagnosis, and the number of treated chest infections in the first two years of life. Body weight (where known) was on average on the 25th percentile at birth in both groups, but it was significantly lower in the unscreened population at 6 months of age. By 2 years the mean body weight of the screened group was at the 50th percentile with the mean weight of the unscreened group remaining on the 25th percentile.

Discussion

Our data indicate the improving sensitivity and specificity of the screening test for cystic fibrosis with advances in the technique, and they provide evidence in support of continuation of the pro-

gramme. The data, however, need to be interpreted with due consideration that the screened and unscreened cohorts were not exactly comparable, and there is the possibility that data from undiagnosed, possibly less severe cases of cystic fibrosis in children who were born during the study period were missed. Because of the age overlap of a number of cases in both groups, the older mean age of diagnoses but earlier birth dates in the unscreened group, and the concurrent management of both groups this was not a sequential study; a fact which disadvantaged earlier investigations. This, plus some data that might have been missed in the unscreened group (by virtue of diagnosis of asymptomatic cases in siblings of index cases diagnosed during the screening programme) gives confidence in comparing progress in the two groups.

We therefore agree, overall, with the conclusion from the only similar published study to date, that neonatal screening for cystic fibrosis reduces morbidity in the first two years of life.⁶ The data

indicate fewer medical attendances, fewer treated respiratory chest infections, and improved overall weight gain in the screened population. We did not find significantly fewer hospital admissions. The number of days in hospital, which have been variously reported as reduced⁶ or increased,⁵ were not analysed. All of our screened patients were briefly admitted for diagnosis for assessment and education about their condition. The later age of diagnosis and possible lesser awareness of the importance of recognising symptoms before diagnosis in the unscreened group might have accounted for the similar admission rates in the first two years of life.

As yet there have been no adequate studies of the psychosocial implications of neonatal screening for cystic fibrosis. The potential effects of the resampling and false positive results⁷ and the effects of diagnosing the disease in 'well' babies have to be considered against the observed findings in this study of repeated medical consultations and delay in diagnosis in a sick child; there is also the advantage with earlier diagnosis of genetic counselling. The psychosocial disadvantages of screening are becoming less obvious now that there is a reduced need for resampling and an increase in the predictive value of a positive result (resulting from more specific assays). There is also increasing experience with the approach to diagnosis in 'well' babies, and conversely the avoidance of delayed diagnosis now that fetal genetic diagnosis is possible.

In conclusion, the published results of screening for cystic fibrosis indicate that screening pro-

grammes deserve wider application and study.^{1 4 6} In particular, as both repeated pulmonary infections and relative underweight are important adverse prognostic indicators in cystic fibrosis, a reduced morbidity should be regarded as one of the primary advantages of screening.

We are grateful to the staff of the cystic fibrosis clinics, Royal Children's and Mater Children's Hospitals, to the Cystic Fibrosis Association of Queensland, especially Drs I Robertson, RM Harris, and Mr E Ryan for providing access to patient records; and to the families of cystic fibrosis patients who provided information.

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Cognitive development in transposition of the great vessels

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SUMMARY Ten children who had had transposition of the great vessels (TGV) repaired, deep hypothermia, and cardiac arrest were examined. Seven children with acyanotic heart disease and 12 unaffected siblings were tested for comparison. Their intelligence, academic achievement, and behaviour was studied. The group with TGV had lower performance subscores on the intelligence test, an increase in somatic complaints, and aggressive behaviour.

Survival of children with transposition of the great vessels (TGV) improved substantially with the advent of balloon atrial septostomy¹ and intra-cardiac baffle.² Children with TGV may have associated hemiplegia due to cerebrovascular accidents,³ or a dyskinetic movement disorder due to anaesthetic hypothermia and cardiac arrest,⁴ or delayed development related to restricted cardiac reserve and chronic hypothermia and parental imposition of restrictions of the child's activities.⁵ The severe neurological damage some children have made us question whether seemingly unaffected

children may exhibit subtle neurological and intellectual deficits.

Subjects and methods

Thirty three children with TGV were treated at the University of Iowa between 1967 and 1984. Four children died. Of the 29 survivors, 14 met the following criteria: age 6.5 to 14 years, no perinatal asphyxia, gestation of >37 weeks, and no associations of mental handicap—for example, Down's syndrome. Two families were untraceable, one family had moved, and one family chose not to participate. A total of 10 children (71% of those eligible) were tested.

Eight children had a Rashkind balloon atrial septostomy followed by the insertion of a Mustard baffle before 2 years of age; this included one child who had a Blalock Hanlon procedure at 6.5 months, followed by a Mustard operation at 29 months. One child had a Waterton shunt at 13 months and a Rastelli procedure at 6.5 months, followed by a Mustard operation at 29 months. Ten operations, one in each child, were performed under deep hypothermia and cardiac arrest. Postoperative complications included one complex arrhythmia that required a pacemaker. Two children suffered a cardiac arrest and were immediately resuscitated. One child required dopamine for circulatory support in the immediate postoperative period. No child had a cerebrovascular accident or convulsion. Two children were thought to have a residual heart disease, and one required revision of his Mustard baffle during the initial period in hospital to repair superior vena cava and pulmonary vein obstructions. One child had late superior vena cava obstruction requiring balloon angioplasty then a vein graft. In six children the postoperative recovery was uncomplicated.

For comparison, children with ventricular septal

defect were selected by criteria identical with those for children with TGV. Of the 14 children who met these criteria, two had moved and one had uncontrolled fits and was mentally handicapped. Three families chose not to participate, therefore eight children were tested (57% of those eligible). All had had a transatrial repair of the defect: two children had deep hypothermia and cardiac arrest; the others were on cardiac bypass for an average of 50 minutes.

Postoperative complications included one child who had a residual ventricular septal defect that required a second operation and one child who had atrioventricular dissociation after surgery that required medical management. None of these children had had cerebrovascular accidents, convulsions, or cardiac arrest.

Seven siblings of children with TGV and five siblings of the children with ventricular septal defect were tested for comparison.

A psychologist who was blind to the design and intent of the study tested all children. He administered the (revised) Weschler intelligence scale for children, a continuous performance task providing an objective measure of fine motor skill, and the Wide Range Achievement Test (a normed reading, spelling, and arithmetic test). Parents completed an Achenback behaviour scale, which is a comprehensive checklist for common behavioural problems in childhood, for which normative data are available by age and sex. A paediatrician interviewed the family and collected developmental milestones from their baby books and school records and performed a general and neurological examination on each child.

The results were analysed by Student's *t* test for making comparisons with population norms. The two groups of children with heart disease were also compared with their siblings using the *t* test for independent samples and for comparing the mean of

Table 1 Mean subscores for IQ from children with transposition of great vessels and three comparison groups of children

	Intelligence quotient		
	Verbal	Performance	Full scale
	(mean (SD))	(mean (SD))	(mean (SD))
Children with transposition of the great vessels (n=10)	93.0 (14.28)	92.0 (9.26)	91.6 (11.98)
Children with ventricular septal defect (n=8)	99.9 (8.75)	99.4 (11.6)	99.1 (9.82)
Siblings of children with transposition of the great vessels (n=7)	95.4 (10.56)	98.0 (17.48)	96.4 (14.42)
Siblings of children with ventricular septal defect (n=5)	102.6 (5.03)	98.8 (12.80)	100.6 (9.10)

Table 2 Academic achievement test subscores of children with transposition of the great vessels and three comparison groups of children

	Wide range achievement test		
	Reading	Spelling	Arithmetic
	(Mean (range))	(Mean (range))	(Mean (range))
Children with transposition of the great vessels (n=16)	90.5 (68-126)	93.9 (68-122)	90.5 (73-105)
Children with ventricular septal defect (n=3)	100.3 (82-127)	106.9 (90-119)	92.1 (72-104)
Siblings of children with transposition of the great vessels (n=7)	112.0 (91-125)	104.9 (98-110)	98.0 (77-115)
Siblings of children with ventricular septal defect (n=3)	105.4 (105-114)	108.0 (88-120)	103.4 (97-115)

the difference between each child-sibling pair. The medical ethics committee of the University of Iowa approved the study.

Results

The mean intelligence quotients of all children are shown in table 1. The only significant differences from the general population were for the children with TGV where three verbal subtests (vocabulary, arithmetic, and comprehension) and three performance subtests (digit span, block designs, and coding) were all below population norm ($p < 0.05$). The mean difference of the sibling pairs' scores showed a significant difference between the group with TGV v sibling pairs and ventricular septal defect v sibling pairs on performance IQ ($p < 0.03$).

The results of the achievement test are shown in table 2. In comparing achievement subscore differences between sibling pairs there was a consistent trend for both groups of children with heart disease to have lower scores than their siblings. For the continuous performance task there were no differences between sibling pairs. On the Achenbach behaviour checklist, the children with TGV were more aggressive ($p < 0.02$) and had more somatic complaints ($p < 0.3$) than did children with a ventricular septal defect. No neurological abnormalities were found for any child. There were no differences in ages at which standard milestones were reached.

Discussion

Our data suggest that children with transposition of the great vessels do have greater impairment of cognitive skills than do children with ventricular septal defect, although in both diseases there is a similar degree of deprivation of stimulation and

potential for exploration because of debility in infancy. These children with TGV did not have impaired academic achievement to a degree equal to the impairment of performance IQ but increase in somatic complaints and aggressive behaviour suggested subtle problems with their peers at school. Interestingly, a degree of social imperceptiveness seems to accompany visual perceptual problems in other populations of children with poor performance IQ and learning disabilities.⁶

With advances in the diagnosis of developmental disorders and advances in educational and remedial treatment of learning disorders it seems timely to begin identifying more specifically the developmental disorder that is associated with a specific disease.

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When is meconium stained liquor actually bile stained vomit?

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SUMMARY Three babies said to have had 'meconium stained liquor' were subsequently found never to have passed meconium. The green discoloured liquor was the result of bilious vomiting in utero secondary to intestinal obstruction.

Case reports

CASE 1

After an uneventful pregnancy during which no ultrasound scans had been performed, a baby boy was born at term, and meconium stained liquor was noted. He fed well and was discharged home after 24 hours. At 4 days of age he began to vomit green, and then brown, smelly fluid. On admission he was severely shocked with gross, tense abdominal distension. After vigorous resuscitation laparotomy was performed; a cavity filled with pus was found in the left upper quadrant caused by an antenatal perforation of the jejunum. Distal to the perforation the bowel was full of inspissated pellets, characteristic of meconium ileus. The colon was narrow and empty. The jejunal perforation was resected and a Bishop-Koop jejunostomy performed. He died 48 hours postoperatively of septicaemia and shock lung. Necropsy showed the histological features of cystic fibrosis.

CASE 2

After an antenatal ultrasound scan at 32 weeks that showed distended loops of bowel a baby boy was delivered by emergency caesarean section because of fetal distress during labour. There was meconium stained liquor. He had a distended abdomen with an umbilical flare and was given antibiotics. Meconium was thought to have been found in the rectum on rectal examination. After intubation he was transferred to the regional unit and after further resuscitation laparotomy was performed; this showed a meconium peritonitis cyst containing 300 ml of brown offensive fluid. There was a volvulus of the jejunum 5 cm distal to the duodenojejunal flexure. The rest of the ileum was normal, but full of inspissated pellets. There was a typical narrow, empty colon. The necrotic loop of jejunum was resected and a Bishop-Koop jejunostomy performed that was closed when the baby was 3 months

old. The diagnosis of cystic fibrosis was confirmed by sweat test, and he was growing well at 12 months of age.

CASE 3

After antenatal diagnosis of a large bladder and bilateral hydronephrosis a baby boy had two vesico-amniotic shunts inserted at 30 and 32 weeks' gestation. Gross polyhydramnios was noted. At delivery at 35 weeks, fresh 'meconium' was noted and the cord was wrapped tightly round him. He required intubation and ventilation for a short period.

On examination he had multiple intradermal haemorrhages on his face from the cord, and the abdominal wall was typical of the prune belly syndrome. Both kidneys and the huge bladder were easily palpable. The initial diagnosis of urinary obstruction by posterior urethral valves was refuted by the micturating cystogram which showed gross unobstructed megacystis without vesicoureteric reflux. Bile stained vomiting started after 36 hours and the diagnosis of megacystis microcolon intestinal hypoperistalsis syndrome was confirmed by barium enema examination (which showed a narrow colon) and by barium meal examination (which showed extremely slow transit into the jejunum). He died shortly afterwards.

Discussion

Meconium stained liquor is a classic sign of fetal distress during labour. The liquor is green or brown and fills the pharynx and stomach, and in some cases the trachea and bronchial tree. Because of the need to ensure that the lungs are clear, paediatricians are called to deliveries at which meconium stained liquor is found so that they may aspirate the trachea either under direct vision or through an endotracheal tube, thus preventing meconium pneumonitis. All three cases reported here were seen by a paediatric team, one before discharge home, and all three before transfer to the regional unit. If the lack of meconium in the rectum in these children with apparent meconium stained liquor had been detected early, it might have alerted their clinicians to the possibility of intestinal obstruction. The operative and radiological findings in each case indicated that meconium could never have been

passed rectally. Earlier diagnosis might have resulted in the survival of case 1, and reduced the morbidity in case 2.

If a rectal thermometer is passed and the end inspected, it not only allows a check on the colour of the rectal contents (if any) but also ensures that any ano-rectal abnormality is detected immediately. The paediatrician called to the delivery should do this himself.

Absence of meconium in the rectum should alert the paediatrician to the possibility that the baby does not have meconium stained liquor, but intestinal obstruction with bile stained vomiting in utero.

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Mercury concentration in cord blood

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SUMMARY The mean mercury concentration measured in cord blood from 51 inner city babies born at Guy's Hospital was significantly higher (37 nmol/l v 20 nmol/l) than that from 17 babies born at the Royal Devon and Exeter Hospital, which serves a more rural population.

The finding of a mercury concentration well above that believed to be 'normal' (from experience with adults) in the cord blood from an infant at Guy's Hospital who died during the neonatal period prompted a literature search for normal values in cord blood. None were found for infants in the United Kingdom, though values are published from other parts of the world, particularly where mercury toxicity is a recognised problem.¹ Analysis, for mercury, of cord bloods from other babies at the hospital (which serves an area of inner London) showed an unexpectedly high mean concentration, this suggested the possibility of environment exposure and prompted a comparison study with infants born in a rural environment.

Patients and methods

Samples of cord blood (5 ml) were obtained from 51 randomly selected babies of normal deliveries at Guy's Hospital from patients living in inner London and from 17 deliveries at the Royal Devon and Exeter Hospital, which serves a rural environment. In both centres the samples were taken from fresh placentas by needle puncture of a placental vein. The specimens were immediately transferred to a heparinised blood tube and stored at -20° until

analysed by one of us (IMH). No information was collected about mothers in relation to possible environmental or occupational exposure to mercury.

Total whole blood mercury was measured by cold vapour atomic absorption spectrometry with a Varian 475 spectrometer by an unpublished method, based on that of Hatch and Ott,² after destruction of the organic material in the samples with a mixture of nitric and sulphuric acids and potassium permanganate. The limit of detection of the method varied between 2.5 and 7.5 nmol/l with a coefficient of variation of 20% at 25 nmol/l. An internal quality control sample that was measured periodically gave a mean (SD) of 50 (2.5) nmol/l. Statistical analysis was by Student's *t* test after log transformation of the data.

Results

Mercury concentrations in cord blood from samples from the rural population were normally distributed about a geometric mean of 20 nmol/l (95% range 11-36 nmol/l). Mercury concentrations in the samples from the inner London population had a skewed distribution with a geometric mean of 37 nmol/l (95% range 10-139 nmol/l) (figure). There was a significant difference between the means of the two groups ($t=9.63$; $df=67$; $p<0.00001$).

Discussion

The pathophysiological importance of these findings is unclear. Mercury toxicity is unlikely below a blood concentration of 1000 nmol/l,³ though Pink disease can be seen in infants and children at

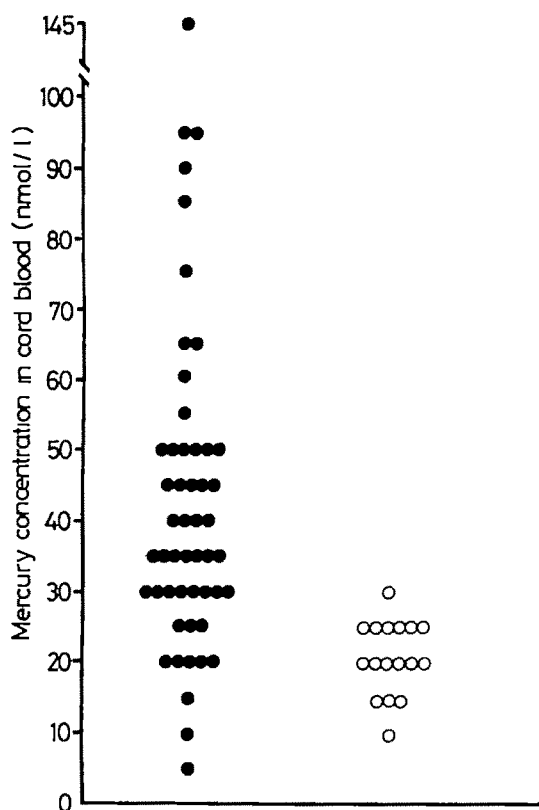


Figure Mercury concentrations in cord blood in infants born at Guy's Hospital (●), and in infants born at the Royal Devon and Exeter Hospital (○).

mercury concentrations considerably below this (unpublished work). It is recommended, however, that the blood concentration of mercury in workers exposed in industry should be below 150 nmol/l. Furthermore, mean concentrations of mercury in cord blood in different parts of the world, vary from 6 nmol/l,¹ to as high as 100 nmol/l.⁴ Organic mercurials cross the placenta much more readily than inorganic salts so that an organic source of environmental contamination should be considered.^{3,4}

Mercury is certainly toxic to the fetus⁴ and its use

in treatment of syphilis increased the rate of abortion.⁵ A relation between the concentration of mercury in cord blood and the incidence of previous stillbirth was shown in a study from America even though the concentrations were low (mean 6 nmol/l).⁶ The correlation was weak and no causality could be inferred. It is also known that placental concentrations of some forms of mercury may be much increased (perhaps 15 fold), compared with cord blood.¹

The Royal Devon and Exeter Hospital serves mothers who live in a small city, with only light industry, or in the country. In contrast, mothers delivering at Guy's Hospital live in one of the most depressed parts of a large city. The differences in environment between the two centres are so numerous that it would be a major task to pinpoint the cause or causes of the presumed increased exposure to mercury occurring in this part of London. There are also many differences in the pattern of morbidity between rural and inner city populations. For example, the incidence of low birth weight is 6% in Exeter compared with 9% in the local population that Guy's Hospital serves. Our observations suggest the need for further studies of concentrations of blood mercury in mothers and neonates born in the United Kingdom.

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Acrocyanosis due to imipramine

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SUMMARY An 11 year old girl who was being treated for enuresis with imipramine developed acrocyanosis of the hands and feet. All biochemical and haematological investigations gave normal results. When imipramine was stopped the girl recovered within three days.

Imipramine, the eldest of the tricyclic anti-depressants, is widely used to treat nocturnal enuresis in children. We describe an unusual side effect of imipramine that has not been previously reported in children with enuresis and suggest a new hypothesis for the pathogenesis of this phenomenon.

Case report

An 11 year old girl was admitted for investigation of persistently cyanosed hands. The problem started seven weeks before admission with sudden painful swelling of the medial two metacarpophalangeal joints of her left hand. The pain lessened but both hands became increasingly blue and swollen. Her feet also became persistently cold, blue, and moist, although not painful. There was no history of cold injury nor of Raynaud's phenomenon.

Her only medication was imipramine 25 mg nightly for primary nocturnal enuresis. This had been started 10 weeks before admission, three weeks before the onset of symptoms.

She was the product of a healthy term pregnancy and normal delivery and had weighed 3760 g at birth. Her growth and development were normal, and her only hospital admission had been for a tonsillectomy and adenoidectomy at age 10. Her father had maturity onset diabetes, and her mother was enuretic until age 16. She had a brother who was also enuretic.

Physical examination showed a slender afebrile girl. Her hands and feet were noticeably cold, blue, and moist, and blanched on pressure. Her forearms showed livido reticularis. Her blood pressure was 120/80 mm Hg, pulse was 80 beats/minute, and all peripheral pulses were palpable. The remainder of the examination was normal.

On admission her haemoglobin concentration was

133 g/l, white blood cell count $7.7 \times 10^9/l$ with a normal differential, and her erythrocyte sedimentation rate was 3 mm in the first hour. The urinalysis gave normal results. A coagulation screen (activated partial prothrombin time, prothrombin time, thrombin clotting time) gave normal results. Cold agglutinins were absent. Rheumatoid factor was absent, as were autoantibodies. Immunoglobulin concentrations were normal. Radiographs of the chest and hands were normal, and barium swallow showed normal oesophageal peristalsis.

During her hospital stay the imipramine was discontinued because her enuresis had not improved. No new drugs were started. Three days later her hands and feet were warm, pink, and dry.

At follow up two months later she reported that apart from one brief episode of cyanosis of the hands on a cold day, her hands and feet had remained normal. She remains enuretic.

Discussion

The diagnosis in this case was acrocyanosis, a condition seen most often in female adolescents and defined as 'a symmetric persistent coldness and cyanosis of the distal . . . extremities'.¹ Acrocyanosis is a vasospastic disorder related to Raynaud's phenomenon, which is intermittent but more severe than acrocyanosis and often leads to trophic changes and ulceration.¹ Childhood Raynaud's phenomenon is rare and is usually associated with a collagen vascular disease.² There was neither clinical nor laboratory evidence of collagen vascular disease in this case. There was, however, a strong temporal relation between imipramine use and the occurrence of acrocyanosis.

There are sparse reports of digital vasospasm attributable to imipramine. Coldness of hands and feet has been observed in two of 52 hyperkinetic children and in two psychotic children treated with imipramine.³ Appelbaum and Kapoor³ have also described an adult treated for depression with 150 mg/day of imipramine who developed digital vasospasm.

A mechanism by which this may have happened is related to the neurohormonal effects of imipramine. Imipramine inhibits reuptake of monoamine neurotransmitters at both central and peripheral recep-

tors⁴: the central blockade is responsible for its antidepressant effect. There is also an anticholinergic effect, which is important in treating enuresis. Finally (and of most relevance in this case) imipramine antagonises both H₁- and H₂-histaminergic receptors.^{4,5}

Digital vasospasm seen in Raynaud's phenomenon, and presumably acrocyanosis, has been variously ascribed to sympathetic hyperactivity or to a 'local fault' within the digital arteries.⁶ Lafferty *et al* have recently suggested that local release of histamine from mast cells may be crucial in the maintenance of digital arterial blood flow.⁶ Histamine acts as a vasodilator while noradrenaline from vascular sympathetic nerve endings acts to constrict digital vessels. We propose that the antihistaminic and proadrenergic properties of imipramine may promote potent digital vasospasm in susceptible individuals.

Whatever the relationship of this vasospastic phenomenon to imipramine, physicians should be

alerted to this disturbing side effect of a drug that is often prescribed for childhood enuresis.

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Transient neonatal hyperthyroidism and maternal thyroid stimulating immunoglobulins

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SUMMARY Serum thyroid stimulating hormone binding inhibitor immunoglobulins (TBII) and thyroid stimulating antibody (TSAb) concentrations were measured in three pregnant women with hyperthyroidism and then in their infants. The results suggested that TBII concentrations in infants in the neonatal period or from mothers during the third trimester of pregnancy showed a good correlation with the development of neonatal hyperthyroidism.

It is now widely believed that the transient thyroid overactivity in infants born to mothers with hyperthyroidism is a result of the placental transfer of thyroid stimulating immunoglobulins from the mother to the infant. The immunoglobulins in the sera from some patients with Graves' disease were shown, by the radioreceptor assay system, to inhibit the binding of thyroid stimulating hormone to its receptor sites and were designated as thyroid stimulating hormone binding inhibitor immunoglo-

bulins (TBII).¹ It was also shown that immunoglobulins in the patient's sera stimulated the production of cyclic AMP in human thyroid tissues and were known as thyroid stimulating antibodies (TSAb).²

We studied three unrelated infants who were born to women with hyperthyroidism, and one of them developed typical transient neonatal hyperthyroidism. We measured serum TBII and TSAb concentrations in these infants and their mothers.

Case reports

Family 1 The mother developed hyperthyroidism at 26 years old when she was in her 32nd week of pregnancy. From the 34th week until delivery she had been maintained euthyroid with methimazole. A girl (3330 g) was born at 39 weeks' gestation. On the 8th day of life she was noted to be hyperactive and had developed diarrhoea. Tachycardia was noticed on the 10th day when her body weight was 3100 g. Thyroid studies on day 8 showed that she had hyperthyroidism; she had serum concentrations of triiodothyronine, thyroxine, free thyroxine, and

thyroid stimulating hormone of 8.6 nmol/l, 527.6 nmol/l, 350.8 pmol/l, and <1.0 mU/l, respectively. Treatment with propylthiouracil and Lugol's solution was started on day 13. Her condition and thyroid function improved gradually and the treatments were stopped on day 59. Her physical and mental development and the thyroid function tests gave normal results at 10 months of age.

Family 2 The mother was first diagnosed as having hyperthyroidism at 29 years old. Two years after the diagnosis she received partial thyroidectomy because of a poor response to antithyroid drugs. After the surgery she had been maintained euthyroid with thyroxine supplement. A girl was born at 39 weeks' gestation. Her development and thyroid function were normal during 10 months of follow up.

Family 3 The mother developed hyperthyroidism at 22 years old when she was four months pregnant. Treatment was started with methimazole but she remained hyperthyroid during the rest of her pregnancy. A boy (2590 g) was born at 39 weeks' gestation and his thyroid function, detected in the cord blood, was normal. Thyroid hormone concentrations gradually decreased until 2 weeks of age when serum concentrations of triiodothyronine, thyroxine, and free thyroxine were 1.3 nmol/l, 47.7 nmol, and 8.0 pmol/l, respectively. The hormone concentrations returned to the normal ranges at 1.5 months of age without treatment. Throughout this period thyroxine binding globulin concentrations were normal and thyroid stimulating hormone concentrations were always less than 1.0 mU/l. At 4 months of age his development and thyroid function were normal.

Methods

Serum samples from the three pregnant women and their infants were stored at -20°C until assayed.

During follow up some of the specimens taken at certain intervals from the same infant were combined for TBII and TSAb assays.

Serum TBII was assayed by the method of Shewring and Smith³ using a commercial kit (Japan Travenol, Japan). Serum TSAb concentrations were assayed by the method of Kasagi *et al.*⁴

Results

In the infant in family 1 who developed neonatal hyperthyroidism, both TBII and TSAb concentrations were high at birth (table 1) and gradually decreased by day 50 (table 2). The concentrations of TBII and TSAb in the mother of this infant at the third trimester of pregnancy were close to the concentrations in the neonate.

The mother in family 2 had detectable TBII and TSAb concentrations in the first trimester of pregnancy and the infant had detectable TSAb but undetectable TBII concentrations in the combined sera obtained on day 4 and 11 (table 1). No TSAb was detected in the infant after the neonatal period (table 2).

The mother in family 3 had detectable TBII and slightly high TSAb concentrations in the second trimester and detectable but further decreased concentration of TBII in the third trimester of

Table 2 Concentrations of TBII and TSAb in the infants of family 1 and family 2 after birth

Age (days)	Family 1					Family 2	
	0	13/17*	27/36*	43	50	4/11*	18/25*
TBII	58.7	45.7	28.0	25.1	23.2	7.9	<6.0
TSAb	5.3	3.4	2.1	1.8	1.6	4.6	0

Control values TBII, <10%; TSAb, <1.0 mU/l

*Serum samples obtained on two different days were combined for assays

Table 1 Concentrations of TBII and TSAb in the mothers during pregnancy and their infants at birth (family 1 and 3) or neonatal period (family 2)

Family	Mothers						Neonates	
	Trimester 1st		2nd		3rd		TBII	TSAb
	TBII	TSAb	TBII	TSAb	TBII	TSAb		
1	*	*	77.2	20.0	54.8	3.4	58.7	5.3
2	33.4	22.0	*	*	*	*	7.9	4.6
3	*	*	20.6	1.8	12.8	1.3	<18.6	0

*Assay not done

Control values TBII <10%; TSAb <1.0 mU/l

pregnancy. Serum of the infant in family 3 at birth had undetectable TBII and TSAb concentrations (table 1). We assume that the transient hypothyroidism in this infant was due to the suppression of secretion of thyroid stimulating hormone as the mother was hyperthyroid during the last half of her pregnancy.

Discussion

One of three unrelated infants born to mothers with hyperthyroidism developed transient neonatal hyperthyroidism. TBII and TSAb concentrations in the cord blood from this infant were high and almost the same as those in her mother during the third trimester of pregnancy. The other infant (family 2) who had high serum TSAb but normal TBII concentrations in the neonatal period did not develop hyperthyroidism and neither did the third infant (family 3) whose TBII and TSAb concentrations in the cord serum were both undetectable.

A recent study reported high concentrations of serum TBII in patients with transient neonatal hyperthyroidism but they did not measure TSAb concentrations.⁵ Another study showed that detectable TSAb in the mother in the third trimester was predictive for neonatal hyperthyroidism, but TBII concentrations were not measured.⁶

In our study TBII concentrations, but not those of TSAb, showed a good correlation with the development of neonatal hyperthyroidism and the concen-

trations of TBII in the maternal sera during the third trimester of pregnancy might have predictive value in the neonatal hyperthyroidism. We think that widespread use of assays for both TBII and TSAb will clarify the pathogenesis and predictivity of transient neonatal hyperthyroidism

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Severe combined immunodeficiency syndrome, tissue transplant, leukaemia, and Q fever

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SUMMARY A child born with severe combined immunodeficiency, who was immunoreconstituted by a fetal liver and thymus transplant, developed acute lymphoblastic leukaemia in the donor cell line. During remission she contracted acute Q fever, which gave rise to unexpected complications. Early treatment of the Q fever might have altered the subsequent events and prevented her death

Q fever is a sporadic infection and is an occupational hazard of men working with domestic sheep and

cattle. The clinical features of the acute and chronic form in adults are well described. Reports in children are rare^{1,2} with less than 50 notifications from 1975-81.³ Heard *et al* reported five cases in immunocompromised adults.⁴ We describe a girl, who was 6 years old at the time of her death, who had been immunoreconstituted by transplantation with fetal liver and thymus at 9 months old because of severe combined immunodeficiency (SCID). Acute lymphoblastic leukaemia (ALL) subsequently developed in the donor cell line. During treatment she developed acute Q fever from which she ultimately died. The advantage of co-

trimoxazole prophylaxis in treatment against leukaemia is well known but its partial effectiveness in Q fever proved disadvantageous.

Case Report

Two girls, the only offspring of healthy parents, were born with SCID. The first died of graft versus host disease after an unrelated marrow transplant. The second child was successfully immunoreconstituted after a second fetal liver-thymic transplant at 9 months of age (the first had failed three months earlier). She remained well and asymptomatic for 21 months when she developed ALL (cALLa and Tdt positive) in the donor cells. At diagnosis the leucocyte count was $10.1 \times 10^9/l$, immunoglobulin concentrations were normal (IgG 7.1 g/l, IgA 1.1 g/l, IgM 1.4 g/l); there was no organomegaly and the cerebrospinal fluid was not affected.

The Medical Research Council UKALL VIII B protocol was used for treatment. Induction drugs were daunorubicin, vincristine, asparaginase, and prednisolone. Cranial radiation and intrathecal methotrexate were used from week 6 to week 9. Co-trimoxazole (150 mg m^{-2}) was used throughout the consolidation and maintenance phase. Despite the unusual history the chemotherapy was tolerated with no infection. Two years from diagnosis while on maintenance chemotherapy she developed an isolated meningeal relapse. This was treated with further intrathecal methotrexate and craniospinal irradiation and the leukaemia induction repeated. Co-trimoxazole prophylaxis was stopped.

Four weeks later she became acutely ill with a high intermittent fever, severe headache, photophobia, myalgic pain in the neck and chest, sore throat, dry cough, and noticeable irritability. A florid centripetal haemorrhagic maculopapular rash appeared. Blood count initially was normal, but fell to $0.5 \times 10^9/l$ with an appreciable lymphocytosis by day 5. Mild hepatocellular disturbance was noted. A chest x ray film was clear. Cerebrospinal fluid examination gave normal results. No significant bacterial or viral isolates were found and a battery of viral titres, mycoplasma titres, and Weil Felix reaction all gave normal results.

After a variety of empirical antibiotic treatments she slowly improved. Co-trimoxazole and maintenance chemotherapy were restarted. Retrospectively, a diagnosis of Q fever was made as the phase II titre peaked (1/512) six weeks later. No specific treatment was given as she was asymptomatic, although the raised titre persisted. Nine months later she developed vomiting, headache, fits, and hemiparesis. Extensive investigations

including examination of the cerebrospinal fluid and computed tomography failed to identify a cause. She was treated with dexamethasone and anticonvulsants as it was assumed she had developed leukoencephalopathy after her previous treatment of the central nervous system. All treatment including co-trimoxazole was stopped. Three weeks later she developed a further exacerbation of the acute influenzal like illness with the central nervous system being affected. Chronic Q fever was suspected despite a normal echocardiogram and no increase in phase I titre. Intravenous tetracycline (continued orally for four months) resulted in a complete and rapid recovery with immediate resolution of phase II titre. Three months later, there was a leukaemic marrow relapse from which she subsequently died a month before her 6th birthday. No further illness attributable to Q fever had occurred.

Discussion

The clinical course of this child's illness was punctuated by three separate events, which were apparently unrelated. Successful immunoreconstitution of SCID with a matched bone marrow donor or a fetal liver and thymus transplant in those without a donor has been recorded.⁵ Prompt restoration and maintenance of immune function after the second fetal liver and thymic transplant was present throughout the preleukaemic and leukaemic phase of our patient's life. The development of ALL in the donor male cells, presumably of fetal origin, has never been previously described. The subsequent course of the leukaemia with a meningeal relapse and ultimately a marrow relapse was perhaps more aggressive than might have been predicted from the presenting (standard risk) features. Optimum chemotherapy doses, however, were well tolerated by the patient's marrow, with no increase in susceptibility to infection until the episode of Q fever.

The unusual features of the Q fever and its chronicity probably occurred as a result of immunosuppressive treatment and partial suppression by co-trimoxazole. The rapid response to intravenous tetracycline and serological conversion can be taken as diagnostic evidence of Q fever infection. The source of the infection was unknown, although an outbreak in the county had been reported four years earlier.⁶ Neither parent, however, had a similar illness or raised titre. Blood products have been suggested as a source of infection, but this child had only received one unit of blood three years earlier. Although Q fever is rare, it is not difficult to diagnose or confirm. With hindsight, we should

have given appropriate treatment earlier because of the persistently high titre. Early adequate treatment might have permitted continuation of antileukaemia maintenance that might have prevented the subsequent marrow relapse that resulted in her death.

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Giving assessment reports to parents

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SUMMARY Reactions of 25 parents to receiving copies of written reports concerning developmental assessment of their children were assessed. All parents wanted to have a written report.

The implementation of the 1981 Education Act has meant that parents now receive a copy of all the assessment documents that contribute toward a statement of their child's special educational needs. Parents also have a right to contribute written evidence of their own about the child. They thus need full information about their child's development.

At the Wolfson Centre children with complex developmental problems are assessed by a multidisciplinary team. After the assessment a full discussion of findings is held with the parents by members of the team. A report is then sent to the referring doctor, and with parent's permission, a copy to other relevant professionals. In general, the practice has been to give a copy of the report to parents only when they request it.

The advantages and possible difficulties of giving a written assessment report to the parents of children with developmental problems have been discussed previously.^{1,2} It has been found that written reports are popular with parents. Similar positive responses have been found when general medical patients have been given copies of hospital

clinic letters sent to the general practitioner.³ In the light of these experiences it was decided to conduct a small evaluation study of routinely sending written assessment reports to parents.

Subjects and methods

Twenty five children seen consecutively by one of the paediatricians (SL) were included. The children's mean age was 5 years 8 months (range 7 months to 11 years 6 months). Their primary diagnostic categories included delayed development (8 children), cerebral palsy (6), speech or language disorder, or both (5), educational difficulties (4), and hyperactivity (2). Most presented a complex picture of disability.

Parents received the same report as was sent to professionals. For 10 children the assessment was conducted primarily by the paediatrician and the report prepared by him alone. For four children the report was written jointly by the paediatrician and a therapist, and for 11 others the paediatrician and the psychologist or therapist, or both, wrote reports separately. In all cases the professional knew the report would be sent to the parents.

Parents were interviewed about their reactions to the report(s), by either HM on the telephone, or the child's health visitor (six cases). Questions were asked about how comprehensible and useful the reports seemed, and also whether they reflected accurately what the parents remembered of the

assessment and discussion (seven point ratings). In addition parents were asked if any technical terms had not been understood, and how the reports could have been improved. The interviews concentrated on reactions to the reports, as distinct from the assessment or the discussion with staff.

Results

No parents refused to participate. Their reactions to receiving reports were overwhelmingly positive. Only three parents gave any ratings below the midpoint (two rated the report as difficult to understand, and one said it was not useful). Eleven mentioned one or more technical terms that they had not known. Only five, however, expressed any anxiety concerning this, and several said they had asked their health visitor or family doctor to explain. Another five parents made more specific critical comments—for example, pointed out minor differences of opinion or stated that the report concentrated too much on what the child could not do.

The 15 completely positive reactions were compared with the 10 parents who had raised any sort of concern or criticism, however mild, on a number of indices, such as age of child, first versus review visit, mode of interview, etc. No significant relations were found (χ^2 or Fisher's test). Two non-significant trends were noted, which may have some validity in this sample. Parents of younger children tended to be more critical than parents of older children. Parents of children with mild to moderate intellectual disability tended to be more critical than parents of children who either were in the average range or had severe or profound intellectual disability. There was no relation between positive reactions and current clarity of definition of the child's problems. Parents' comments on the usefulness of the report are shown in the table.

Discussion

Any conclusions from this small study must neces-

Table Parents' comments on usefulness of written reports

Categories	Frequency
1 Jog memory—too anxious at the time to take all in	11
2 Can look back and read again in future and see progress made	8
3 Can 'mull over' what has been said	5
4 Can discuss with husband and family	5
5 Can discuss with professionals	5
6 Outside view, different angle helps you to stand back and pinpoint areas where child needs help	5

sarily be tentative; however, they parallel conclusions of previous articles. Firstly, reports are popular with parents. Secondly, parents of older children—that is, those who may have had longer to think about and accept the nature of the child's disability—tend to be more positive. Thirdly, technical terms require explanation, either in the body of the report itself, or by encouraging parents to discuss the report fully with the relevant professionals. Fourthly, as was also found in the Warwick evaluation,² numerical results of assessments can be sent to parents, suitably presented and discussed, without raising alarm.

A number of professionals, particularly doctors, have strong reservations about sending written reports of complex assessments to parents. Many reservations are justified, but may imply the need for an alteration in procedure rather than not sending a report. For example, where a professional needs to make additional points to a colleague (for example, raising the question of a possible diagnosis more severe in its implications than those already suggested), a covering letter can be sent with the report. Discussion of the assessment with the parents is valuable in itself and aids understanding of the report.

It is relevant to consider circumstances in which a written report may be unhelpful. For example, where a very young child with multiple impairments comes for initial assessment the clinical role of the assessment team includes finding ways gently to impart information to parents and to help them assimilate it. A written report may be premature, whereas helpful suggestions concerning treatment based on shared observations may be better received. As parents become aware of the extent of the child's disabilities, and educational services begin to be involved, written reports will then become appropriate.

Thus, with reservations about particular circumstances, it seems that giving assessment reports to parents has clear benefits. It helps parents to recall in detail information and professional opinion about their disabled child over time. It aids discussion with professionals as it is clear to all what information has been shared with parents.

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Controversy

Conductive education for motor disorders: new hope or false hope?

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Parents of children with handicaps naturally want the best available treatment for them. If progress is slow or the handicap severe the parents often become frustrated and seek alternative forms of treatment. This quest may be triggered off by family and friends, professionals, parents' groups, or by the media. In April 1986 a documentary entitled *Standing up for Joe* was broadcast. It described how Joe with cerebral palsy, described as untreatable in this country, was taken by his parents to the Pető Institute in Budapest where his parents were inspired with hope for his motor rehabilitation. This was to be achieved using conductive education, a form of education for children and adults with motor disorders available only in Hungary. British medical and therapeutic services were portrayed as depressing and apathetic and the Hungarian Institute as inspiring, determined, and successful. Children with motor disorders in Hungary were shown moving, walking, and playing and—in one particularly emotional shot—walking off into the sunset!

Although all this makes effective television, it has an unjust and destructive element. Parents of children who will never walk are challenged and threatened by an illusory hope. Morale among therapists is shattered as their work is dismissed without regard for their skill and dedication. Despite this we should not ignore the important questions which are raised by such media coverage. Parents have a right to ask whether conductive education represents a major advance in treatment for children with motor disorders.

Three quarters of the children leaving the Pető Institute achieve 'orthofunction'—implying that they can walk and manage stairs and toilets in a normal school or other social setting appropriate to their age.¹ This widely quoted statistic means little, because selection of suitable patients for conductive education and treatment at the Pető Institute could easily ensure such a result, and there is no doubt that selection does occur. It is known from the

Hungarian statistics that children with considerable mental handicap do not respond well to conductive education. Data concerning audit of outcome for children with handicaps in this country, however, are collected sporadically and are not generally available to parents or professionals. Controlled trials comparing conductive education with other forms of management in motor disorders of childhood are not available. There is, however, little scientific evaluation of our present treatment of motor disorders, so it is not reasonable to dismiss conductive education because of lack of scientific studies.

Conductive education

The system of conductive education was started after the Second World War by the late Dr Andras Pető and has been developed by Dr Maria Hari. As a complete educational system for those with motor disorders it cannot be described in a few sentences. Nevertheless, it is valuable to contrast some of the practices of conductive education with the conventional British management of motor disorders. Children receiving conductive education may receive daily lessons in groups from an early age. The approach seems intensive with a firm emphasis on independence, but visitors to the Institute have usually commented on the cheerful and positive atmosphere. Children of kindergarten age may be admitted for residential treatment. Conductive education is supervised at all times by 'conductors'. These professionals are carefully trained in the techniques of conductive education in a four year programme. Children are motivated and expected to achieve and maintain motor independence. There is emphasis on breaking motor tasks down into simple steps, on problem solving and goal directed activity, and on the use of rhythm and music to aid in learning motor skills.

Conventional treatment

By contrast, the accepted British view of treatment is less intensive. Physiotherapy is usually the mainstay and begins at the time of diagnosis. Mothers and babies are usually seen together for a few hours each week. Parents are taught how to handle the child and to encourage good postures. Various developmental treatments may be selected, depending on the nature of the motor disorder and the aptitudes of the therapist and the parents. Suitable seating and play material are introduced, often with the help of an occupational therapist. Parents are encouraged—indeed expected—to work with the child each day to promote desirable motor activities and postures. Emphasis is placed not only on treatment but on care of the whole family. Recognition of the importance of play, relaxation and forming satisfactory relationships with mother and other family members are important early goals. As children grow older they may well be offered a place in a treatment group but this usually only meets for a few hours once or twice a week. During development they may well have treatment from other therapists including speech therapists and psychologists. These professionals integrate their activities through a multidisciplinary team.

Discussion

Clearly these two approaches vary in their philosophy and their practice. The British approach emphasises the role of the parents and the family. Children are kept in their own homes and the family is preserved as a functioning unit, much of the burden of developmental treatment falls on the family. Some are well able to respond—others less so. The Hungarian approach is centred on the child and his or her needs to obtain motor skills. Responsibility for the child's education is removed from the family. The child spends hours, days, months, or even years away from the family during the process.

To the paediatrician the cost of conductive education seems high in terms of disruption of family life and normal childhood, especially as many children with motor disorders do well on the treatment they receive in their own homes. At the same time there are doubts. Do families feel that they are not supported enough and left to solve problems too complex for them? Are families of handicapped children able to be firm and determined with them in expecting development of motor skills? Are there children in wheelchairs who would be walking if we had been determined advocates of more intensive treatment for them? Is the cost of conductive education on repaid in terms of improved results?

While we sit and ponder a considerable bandwagon for conductive education is beginning to roll. A national movement, Rapid Action for Conductive Education (RACE) has been formed as a pressure group to lobby politicians, educators and doctors; 200 parents and sympathetic professionals attended the RACE national conference in April. The meeting was like a political rally. Dr Hari came from Budapest for the meeting and was greeted enthusiastically; parents whose children have received conductive education in Hungary told of their successes, but other parents seemed angry and frustrated. British resources were again criticised for being totally inadequate. A determined and articulate lobby seems likely to develop, demanding that conductive education be made available in Britain.

Even if this were desirable is it feasible? Conductive education is not new. Over the years many visitors to Budapest have brought back reports on aspects of the technique. In particular, Ester Cotton introduced the technique at Inglefield Manor (a Residential Spastic Society school) in the early 1970s; training courses in conductive education have been held at Inglefield ever since. Various teaching methods styled 'conductive education' have been tried with varying degrees of success in institutions around the country, but this has not constituted a major advance in treatment. It is now claimed that in order to succeed conductive education must be taken as a complete philosophical and educational package. This seems to imply that 'conductors' should be trained in Budapest and children of adequate intellectual potential should be educated intensively from a very early age. Such a scheme is being implemented by Andrew Sutton and his colleagues in Birmingham (The Foundation for Conductive Education—Sutton, personal communication). This programme will involve a group of English children and trainee 'conductors' who will work in Birmingham with help from their Hungarian counterparts and they will also spend time in Hungary during a four year course. They hope to study a control group simultaneously. This attempt to transcribe the Hungarian approach into an English setting should help answer fundamental questions about the value of the technique and the feasibility of establishing the Hungarian system in its entirety in the different cultural background of this country. Unfortunately, the results of this study will not be available for some years.

In the meantime media presentations and parents' groups encouraging conductive education may simply increase frustrations. Parents are shown a wonderful and yet mysterious treatment which is only available in a distant country. Even the enthusiasts say it cannot be brought to this country

without a prolonged gestation period, which is only just beginning. It is not surprising therefore that irritation and anger may be the result, emotions which may be directed at doctors and therapists managing the children. What response should we make? Firstly, we should be working not only towards excellence in developmental services but also to get services for motor disordered children portrayed in a more positive light. Many children receive excellent treatment from teams of dedicated professionals. Children are treated in their own homes because we believe in the importance of the family for the satisfactory psychosocial development of children. The nature of developmental therapy in this country reflects a real belief in the value of mother/child interaction and the power of parents to bring out the best in their children. It does not usually reflect apathy or lack of care.

We should keep an open mind about new treatments and we should support The Foundation

for Conductive Education and await the results of their trials with interest. Of course some families and children do not get satisfactory development treatment: no two families are the same, and in some families a more intensive approach is justified. In that case we should be fighting for extra therapeutic resources on their behalf. A tide of enthusiasm for improved treatment for motor disorders from the media could then be harnessed to a more achievable goal than the elusive one of conductive education

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Conductive education

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At a technical level there is little particularly surprising about conductive education. Neuropsychologically it exhibits the plasticity of human cerebral functioning.¹ Developmentally it illustrates the principle of the sociogenesis of mind² and the role of activity in human mental development.³ Pedagogically it shows in yet another field of special education that apparently insuperable barriers to developing proper function may be surmounted by optimistic inspired, and thoroughgoing educational provision.^{4,5} All in all, it is therefore surprising—and telling—only that it has not been tried here before. That it has been tried elsewhere, however, and the fact that news of this is now in the widest public domain, is currently cause for concern among many professionals working with motor-disordered children. It can at times be hard to disentangle whether this concern responds to the substance of the system or to the manner and speed with which it has entered the public consciousness and to its possible implications for current practice.

Only a couple of years ago it was right impossible to generate interest in what was still regarded, despite glowing earlier reports, as an unlikely and novel approach. Conductive education remained virtually unknown in British special education and paediatrics, with those who did know of it often ready to cite experience or evidence to suggest that it promised little or no advantage over existing approaches. Very suddenly the picture has altogether changed. In 1985 and early in 1986 British families began to take their motor-disordered children to Budapest in rapidly growing numbers, to join families from a number of other countries and test this system for themselves. The process was mightily hastened, though most certainly not initiated, by the showing of the television documentary *Standing up for Joe* on 1 April 1986; whereafter over 100 British families have obtained places for their children at the Petö Institute in Budapest. Growing national interest was fuelled by reports of this *Völkerveränderung* in local and national press, and on local and national radio and television. The pressure group Rapid Action for Conductive Education (RACE) was formed a few

days after *Standing up for Joe* and, by the time that this article appears in print, will have already staged two mass lobbies of parliament to voice its demands.

Events do not usually move so fast in British disability. Existing institutions, voluntary, professional, academic, statutory, and governmental, have been rather caught on the hop. Small wonder then that myths and misapprehensions abound in the place of hard fact and clear analysis. Dr Beach has presented a most fair statement of the dilemmas that this sudden upsurge of events has created. He does, however, seem to share some current confusions. I shall not comment upon his ikon of present British provision for motor-disordered children, which he paints as smooth, coordinated, goal-directed, client centred, and effective. I shall restrict myself solely to outlining vital facts as I see them on conductive education in its country of origin and on attempts to establish it outside that country, along with my own suggestions for how progressive professionals might respond to the undoubtedly unsettling challenge that this system must throw down to their existing practice.

Conductive education

Conductive education for the motor-disordered is precisely what it says: an education. It is not a therapy. Neither is it a 'cure,' a means of nursing chronic invalids, nor a welfare provision for the disabled. It is a system of educating children who are unable to control their bodily movements (and, though this will not be discussed further here, adults who lose such control in later life), with the goal of establishing a high degree of independent function.

Relevant conditions in childhood are cerebral palsy and spina bifida. The outcome, 'orthofunction,' is readily indexed in Hungary by children's admission to the school system at a level appropriate to their mental potential. In Hungary, as in most advanced countries, school children follow a national curriculum. But there are no resources nor even the rhetoric for integration as advocated here. To fit into their rigorous school system pupils must be mobile, continent, able to

care for themselves physically, and capable of working and studying along with the rest. As far as one can tell from the official returns, around two thirds to three quarters of pupils leaving the Pető Institute each year go on into the school system and, with varying degrees of follow up support, continue there. What one cannot tell is how far the Pető Institute is successful in its mandated aim of reaching all potentially eligible children in the country.

Children are ineligible if they are unable to participate in the educative process: this particularly includes children so profoundly mentally handicapped or so autistic that it proves impossible to establish communication with them and generate their active collaboration in what is being done. Figures for 1983 showed that 15% of children registered were thus ineligible. Pupils whose mental incapacity is less total *are* eligible (despite frequent assertions in this country to the contrary), though educational goals will of course be different. Thus a severely mentally handicapped pupil will not be taught to read and write, and the process of learning mobility and other basic functions will take longer than in a child of normal mental potential.

The intention in Budapest is that children should be placed on the national register of motor-disorders as soon as the condition is identified. Parents should then attend a 'parents' school' for advice on how to relate and respond to their child. This will be followed by attendance at a mother-and-baby group (fathers go too, sometimes), two or three two hour sessions each week in which parents and children work together as units. Thereafter there are day and residential kindergartens to age 6, day and residential schools to around 11 years (residential provision is fortnightly, term time only), as well as a variety of visiting and follow up services. It is a rare child who attends right through the system. If started young a child might take a couple of years or so to orthofunction. Starting later slows the process, as do unfavourable mental factors, and the pace varies according to physical condition (for example, children with athetosis generally take longer). And as elsewhere, the system of identification is not foolproof, as witnessed by the urgent parental referral of previously unknown children after the screening of the Hungarian language version of *Standing up for Joe* on 1 July 1987.

The educational philosophy bequeathed by András Pető, the founder of the system, is termed 'conductive.' This holds that pupils must want to learn, set their own goals, and find their own way of solving them. Emotional and motivational factors are therefore a cardinal and central concern of those who teach. The teachers' role is to conduct

their pupils carefully into and through the process of learning—hence 'conductors.' The focus of conductive education for the motor-disordered is therefore primarily upon the mind of the learners, its conative as well as cognitive spheres. The whole process depends upon a close interpersonal relation between teacher and taught, upon a teacher with considerable insight (the 'warmth, empathy and genuineness' of the good psychotherapist), and upon the particular motivational force of the group.

It has been commented on by recent foreign visitors to the Pető Institute that specific motor techniques observed differed little from many of those used by, for example, British physiotherapists. The Pető Institute does indeed appear to pay close scrutiny to foreign approaches for what might be learned from them. The conductive education system, however, incorporates higher-order features—for example, a developmental theory based upon social-psychological principles, a classroom and school organisation that unify the mental with the motoric and make their development a priority over all other institutional requirements, and above all there is the particular moral commitment to children's progress that permeates the system.

According to viewpoint, one may regard the above as hyperbole, or no more than a statement of bases common to all great pedagogies, special or otherwise.

Attempts to establish conductive education outside Hungary

Cotton's seminal article introducing Pető's work to the English speaking world⁶ was not followed by the major institutional commitment required to introduce this complex system over here. Lacking such support from either state or voluntary sector, Cotton and her immediate associates developed a personal practice on the basis of what had been observed in Budapest. In the early seventies a local authority day school, Clairmont in Bristol, attempted to turn itself over completely to this basis but unfortunately no record of this work passed into the public domain. A Spastics Society residential school, Ingfield Manor, also took up the work but a series of studies carried out by the Institute of Education failed to show advantage over the conventional approach (A McCormack. *Conductive education reassessed*. Unpublished MSc dissertation, University of London, 1974). Nevertheless, a specialist 'Pető Unit' opened at the school in 1976 and has served as the canonical image of conductive education throughout the western world. Moreover, through short training courses, the methods used there spread this new practice to a

number of settings in the United Kingdom and overseas.

This new practice has tended to assume the name conductive education. From the outset, however, Cotton was emphatic that the core of her approach, the 'basic motor pattern', was *not* conductive education but an adaptation of what she had seen in Hungary to suit the exigencies of her British circumstances—'The expression 'basic motor pattern' was not used by Professor Pető. I have developed this concept during many years' work and close cooperation with Dorothy Seglow.'⁷ Working within from the existing institutional base introduced a further new principle 'the unity of disciplines': the notion of a specialist teacher, the 'conductor', was abandoned in favour of a confederacy of various professionals ready working together. Realistically, the goal of this new system was quite different from that of Pető—'It is hoped that after further periods of treatment the children will be able to enter special schools where, as a result of conductive education, they will be able to benefit more fully from the teaching and hold their own with their less severely handicapped peers.'⁸ The Pető Unit has yet to show itself successful in gaining this limited goal (L Jernqvist, Preliminary education of conductive education, Spastics Society, London unpublished report, 1980). Substance and goals notwithstanding, however, the term conductive education continues to be used for such programmes, with claims made to be exercising the 'principles of conductive education' without reference to its philosophical or organisational bases.

Until recently only Japan has sent staff to Budapest to train as conductors and establish a system to implement conductive education (though as yet there have been no published reports to describe how this Japanese work is progressing). International interest in the Pető Institute has grown apace in the last few years, and a number of other countries have tried or are trying to set up schemes. The United Kingdom has been fortunate in winning the formal collaboration of the Pető Institute to train conductors and establish working groups of children and adults. A new national charity, the Foundation for Conductive Education, has been established to work with the Pető Institute: its first main project, the Birmingham Institute for Conductive Education, began on 1 September 1987. Central to this work is research into the system, to define its outcome and limits, and to identify its essential active ingredients

Hope

It will take a long time for the Foundation, working

in conjunction with the Pető Institute, to set up conductive education in the United Kingdom and it will be some years before unequivocal answers are available to even some of the host of questions about the system that are now being reasonably posed by parents, professionals, and politicians. In the meantime the very process of establishing this work over here will inevitably contribute to the upward spiral of public attention and demand. In the circumstances parents cannot be expected to be other than hopeful of what might be achieved by the Hungarian system, critical of what their own children are receiving, and upset that they do not have the possibility of a choice. Rightly or wrongly, awareness of conductive education is likely to have a continuing and powerful impact upon all involved in services for the motor-disordered, in health, education, and welfare. What, at this early stage in a rapidly developing situation, might those services do in response?

Dr Beach suggests one strategy: to push for an extension of resources for existing provision, riding the tide of media interest in motor disorders. This, he considers, may be a more achievable goal than 'the elusive conductive education.' The strategy of more of the same might indeed attract some spin off. On the other hand, the tide might prove very hard to divert, given the limited goals and uncertain effectiveness of paediatric physiotherapy.⁹ At the moment *any* kind of inclusive and adequate service for motor-disordered children and their families seems an elusive goal and, despite a considerable start, there seems no *a priori* political reason to expect existing systems to expand to fill the void. Perhaps an awareness of this contributes to a continuing appropriation of the term conductive education by schemes in both the voluntary and statutory sectors.

There is another response, which in no way denies the attempt to upgrade existing services but which ought to coexist with it for the longer term benefit of all, providers and consumers alike. Firstly, professionals working with the motor-disordered ought to acquaint themselves as fully and as factually as possible with what is known of conductive education in its country of origin. There is some extraordinary nonsense talked about conductive education and at the very least parents deserve informed and professional information when they discuss this issue with their medical and educational advisers. Secondly, professional advice should include a clear appreciation of what is going on over here, make distinctions based upon the substance of schemes rather than their names, and know the clear objective reasons why conductive education, whatever its virtues or demerits, cannot be made avail-

able immediately for everyone who might ideally benefit.

Thirdly, and most substantially, professionals might look at some of the universal bases within conductive education, suggested in the opening paragraph of this article, and question whether these serve as grounds to re-examine their own practice. This is not to advocate naive attempts to ape reported aspects of what is done in Budapest. On the contrary, it is to suggest genuine indigenous innovation, such as is already occurring in some schools for the physically handicapped, in direct response to the challenge of conductive education. Two such schemes, begun in 1987 and known by the inevitable special educational acronyms, are INSTEP (Independence Skills Through Education Programmes) at Ormerod School and FLAME (Function, Language and Motor Education) at Lord Mayor Treloar College.

In the meantime, what to do about hope, be it new, false, or illusory? Perhaps one should remember Claudio in *Measure for Measure*: 'The miserable hath no other medicine . . . '

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Human retroviruses and paediatric disease

Sir,

Thomson and Dalgleish discuss the management of human immunodeficiency virus (HIV) positive children with regard to immunisation and state that 'HIV positive children should never be given live viral vaccines'. In a review of the medical records of 213 children with symptoms of acquired immune deficiency syndrome (AIDS) or AIDS related complex (ARC), 171 had been immunised with live oral polio vaccine and 63 with measles mumps, and rubella vaccine with no adverse effects. At least 38 of them received live vaccines after the onset of symptoms related to HIV.² In addition, of the 71 children followed up in the European collaborative prospective study of infants born to mothers positive for HIV, 56 had received diphtheria/tetanus or diphtheria/tetanus/polio vaccine (DTP), 33 Salk, 14 Sabin, eight hepatitis B, and one mumps vaccine. Of the five children who had developed AIDS or ARC, two had received DTP, two Salk, and one Sabin vaccine. No adverse reactions were reported in any child.³

The potential benefit of protecting these children from natural disease before their immune system is compromised led the World Health Organization and the Immunization Practices Advisory Committee of the US Public Health Service to recommend that DTP, oral live polio, and measles vaccines should be given to asymptomatic children infected with HIV.²⁻⁴ Live vaccines (oral polio, measles and BCG) should only be withheld from children with symptoms of AIDS or ARC because of theoretical concerns about the competence of their immune system. Children, however, who live in a household with patients with AIDS or ARC should be given inactivated polio vaccine instead of oral polio vaccine because of the risk of secondary transmission. With regard to immunisation of infants positive for HIV, it is important therefore to distinguish between those who have symptoms related to HIV infection and those who do not.

All available information must be used before reaching decisions which will have far reaching implications, and we urge that caution be exercised before statements are made which may influence policy.

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Sir,

Thomson and Dalgleish¹ give advice on the immunisation of HIV positive children that is at variance with current practice and likely future official recommendations. They do not distinguish between children who are HIV positive but asymptomatic, and children who have developed clinical AIDS with associated immunodeficiency. In advising that 'HIV positive children should never be given live viral vaccines or BCG' they omit any reference to pertussis vaccine, which as a killed vaccine can be used with safety. Furthermore, recent experience suggests that:

(1) Even symptomatic HIV positive children may be given live vaccines with the exception of BCG, as the benefits of protection appear to outweigh any risks from the vaccines. Inactivated vaccines should also be given in accordance with existing recommendations.

(2) Asymptomatic HIV antibody positive subjects may be given live vaccines for appropriate indications with the exception of BCG. If their parents or other household members are known to be immunocompromised (from AIDS or any other reason) the children should not receive oral polio vaccine because vaccine viruses are excreted by the recipient of the vaccine. These children should receive inactivated polio vaccine for routine immunisation.

(3) Children and young adults with AIDS or other clinical signs of HIV infection may be at risk of serious complications of infectious disease such as measles or varicella. If they are exposed to these diseases they should be given passive immunisation with appropriate immunoglobulin.

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Dr Thomson and Dalgleish comment

We would like to thank Dr Senturia, Professor Peckham, and Dr Campbell for drawing attention to the controversial advice pertaining to live vaccines and HIV infected children in our annotation. The advice we quoted for the

HIV infected subject has many advocates in Western communities.¹ The situation is, however, clearly different in countries where the risk of the vaccineable disease is not only high but also carries a high morbidity and mortality. Moreover the complete or partial cessation of the World Health Organisation (WHO) extended programme for immunisation because of fears of vaccinating HIV infected children would be disastrous for many countries. We did not emphasise the difference between asymptomatic HIV positive children and those with AIDS or AIDS related complex, as we had already made the point that the distinction is more difficult to make in children.

At a recent WHO meeting (11–13 August 1987) attended by AGD these issues were reviewed. There is a vast and increasing number of reports that suggest that activating or stimulating T cells in vitro may lead to increased replication of HIV. Although many aspects of HIV infection in vitro can readily be extrapolated in vivo, all the available evidence (much of it unpublished) suggests that multiple vaccinations of HIV infected children do not appear to be detrimental although it is likely that HIV infected children only respond to neoantigens before they become symptomatic. A full review of these data by WHO advisers supports the use of antigens in HIV infected individuals in those countries where the target diseases of the extended programme for immunisation remain important causes of morbidity and mortality. No distinction was drawn between asymptomatic children and those with clinical AIDS, reflecting the overwhelming importance of continued vaccination programmes in these communities.

The antigens recommended for the extended programme for immunisation include the live viruses vaccines—measles and polio, the toxoids—diphtheria, tetanus, and pertussis (DTP), and BCG. The inactivated polio vaccine is preferable to the oral preparation where possible, although the oral preparation is far cheaper and more widely available. All vaccines should be given to all children as early in life as possible in countries where HIV is endemic, especially as screening of all children may be impractical before vaccination. In areas, however, in which tuberculosis is uncommon BCG may be withheld from those children known to be HIV seropositive and should definitely not be given to those with AIDS or AIDS related complex.

We thank the above correspondents for pointing out that the word 'never' was inappropriate in the absence of a more detailed discussion.

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Aetiology of growth hormone deficiency

Sir,

We were interested in the report by Herber and Kay on the aetiology of growth hormone deficiency.¹ We have

recently reported a small study that in part addresses the pathogenesis of hypothalamopituitary damage due to birth injury and hypoxia.²

We studied 26 consecutive children with newly diagnosed idiopathic growth hormone deficiency. Twelve children had perinatal problems that we believe either led to or reflected trauma, hypoxia or ischaemia. Of these 12 children, 11 had an empty sella turcica on high resolution computed tomograms of the hypothalamopituitary region. We found a highly significant association between an empty sella turcica and such perinatal problems and between a full sella turcica and no such problems. In addition, an empty sella turcica was significantly more likely to be associated with multiple pituitary hormone deficiencies and a full sella turcica with isolated growth hormone deficiency.

Although our sample size was smaller than that of Herber and Kay, we were able to obtain details of perinatal events directly from our subjects' parents and from their case notes. We believe our results indicate that (idiopathic) growth hormone deficiency may be precipitated by events around birth compromising the blood supply to the pituitary gland and resulting in the empty sella turcica on computed tomograms.

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Sir,

We read with great interest the paper by Herber and Kay.¹ We are, however, surprised by the conclusion that the strong relation noted between traumatic deliveries and subsequent growth hormone deficiency no longer exists in the United Kingdom.

We recently analysed some perinatal risk factors in 177 patients in Belgium with growth hormone deficiency.² We found that the frequency of non-cephalic fetal presentation was about eight times higher in patients with growth hormone deficiency (31%) than in the control population (4%). The difference is highly significant ($\chi^2=47$, $p<0.001$).

Herber and Kay were unable to examine breech deliveries separately. We therefore suggest that due to this limitation in their study they are unable to draw conclusions about traumatic delivery and subsequent growth hormone deficiency. In our study all children with breech

presentation were delivered vaginally and spontaneously, suggesting a pituitary insult during vaginal delivery. Isolated growth hormone deficiency was also often found in association with induction of labour. These data and those reported elsewhere indicate that even a mild birth trauma may result in growth hormone deficiency.^{3,4}

We therefore stress that non-cephalic presentations are definitely an important risk factor for the subsequent development of growth hormone deficiency. Postnatal growth should be monitored carefully in these infants in order to detect early growth impairment due to growth hormone deficiency.

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Sir,

We read with interest the paper of Herber and Kay¹ about the perinatal risk factors for the development of growth hormone deficiency.

We report a study of 99 children (72 boys and 27 girls) admitted to our clinics with growth hormone deficiency. The mean (SD) age of boys was 11.5 (4.1) years and that of girls 11.7 (4.7). The ratio of boys to girls was 2.67:1, similar to that reported by Rona and Tanner.² In our study the percentage of premature deliveries was higher than that in the general population ($p < 0.01$), confirming the observation of Herber and Kay. We did not, however, find a significant difference between the gestational ages of boys and girls. As previously reported, we found a high percentage of breech deliveries (39%).³ The mean birth weight of children delivered at term was 3310 g (0-65) for boys and 3070 g (0-60) for girls. Compared with national data, girls were significantly lighter ($p < 0.01$), and boys had a mean birth weight within the normal range.

In conclusion, our experience in an Italian cohort partly confirms and adds further evidence to the findings obtained by Herber and Kay in the United Kingdom.

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Psychological adjustment and diabetic control

Sir

I was interested to read the evidence presented by Fonagy *et al.* suggesting that indications of psychological disturbance in diabetic children and their parents predicted lower concentrations of glycosylated haemoglobin in the children's blood.¹

We published a study last year² in which we similarly showed that contrary to expectation and popular dogma diabetic children who seemed potentially depressed and had low self esteem had better glycaemic control as reflected by the concentration of glycosylated haemoglobin. Apart from the central finding that poorer psychological indices are associated with better glycaemic control, there are two other similarities between the studies. Specific symptoms of emotional compared with behavioural disturbance correlate better with low glycosylated haemoglobin concentrations. We also noted an external locus of control in this subgroup of children (a person with an 'external' locus of control believes that his own actions have little effect on his destiny, and that other people or other forces control what happens to him). Fonagy *et al.* showed that diabetic children who were perceived as being less independent and less responsible for their own treatment had better glycaemic control.

The clinical lessons from these studies, however, are difficult to decipher. I am sure one should still strive for excellent biochemical control on the one hand and good diabetic adjustment (the psychosocial condition of the child) on the other and not assume that the two objectives are mutually exclusive. Perhaps those who seem to achieve good biochemical control should be assessed in terms of emotional well being and happiness and given appropriate psychological support and advice, and one should intensify efforts to improve the techniques of the happy well adjusted diabetic who has a high glycosylated haemoglobin concentration. I am, however, doubtful whether there will be a pronounced improvement in the management of diabetic children until the physical means of treatment are not dependent on such a high and unnatural degree of compliance.

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Dexamethasone in bronchopulmonary dysplasia

Sir,

Dexamethasone is useful for the treatment of bronchopulmonary dysplasia in premature infants and it is likely that its use will increase. Several side effects have been reported, including an increased incidence of infection. Because glucocorticoids are known to produce neutrophilia in adults (probably through a combination of increased release of neutrophils from the marrow, and prolongation of their circulating half life), and because neutrophilia is sometimes an indication of infection in the newborn, it is possible that a false suspicion of the presence of infection may be raised in babies being treated with steroids. We describe the neutrophil counts of eleven babies whom we have treated with steroids during the past year.

Each baby was treated with 0.6 mg/kg/day of dexamethasone for one week. The table shows the neutrophil counts before and during the period of treatment with steroids. In four babies a pronounced neutrophilia ($>20 \times 10^9/l$) developed during treatment. In three of these the blood film was reported as shifted to the left with a band neutrophil:neutrophil ratio greater than 0.25:1. In two babies a left shift with an increase in band neutrophil:neutrophil ratio occurred in the absence of neutrophilia. None of these babies showed other signs of infection, no pathogens were grown on serial blood

cultures, and C reactive protein estimations yielded negative results.

We recognise that neutrophilia alone is not a sensitive indicator of infection however pronounced it is, and an increase in the proportion of immature neutrophils is bound to raise the suspicion of infection. We report our experience to make the point that this may occur as a result of the treatment of premature babies with steroids as it does in adults.

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Giving drugs per rectum for systemic effect

Sir,

I read the annotation by Dr Choonara with interest.¹ To prevent paraldehyde given rectally, however, from being prematurely considered as part of the history of anti-convulsant treatment I should like to make the following points.

In Canada and the United States of America it remains current practice to give paraldehyde rectally in the treatment of status epilepticus,^{2,3} and 83% of the dose given this way is absorbed.⁴ Absorption after intramuscular administration depends on blood flow within the muscle; in a child having convulsions this may be reduced and absorption therefore delayed.

A 50% solution of paraldehyde given rectally infrequently produces intestinal irritation and rarely causes perforation of the large intestine. An intramuscular injection results in extreme pain at the site of the injection and sterile abscesses, fat necrosis, sloughing of the skin, and muscle irritation have occurred even when the drug is injected deep within the muscle. Severe and permanent nerve damage has occurred when the drug has been injected too close to nerve trunks.⁴ The frequency and severity of these complications militate against the use of paraldehyde intramuscularly. Finally, paraldehyde produces less respiratory depression than do the benzodiazepines.

In an emergency department in which intravenous access is not readily available, an emulsion or solution of diazepam given rectally may well be the preferred treatment of status epilepticus. Paraldehyde given rectally offers a safe and effective alternative. There is also

Table Neutrophil counts in 11 babies treated with steroids

Case No	Gestation (weeks)	Age (weeks)	Maximum neutrophil count during seven days before treatment with steroids ($\times 10^9/l$)	Maximum neutrophil count during treatment with steroids ($\times 10^9/l$)
1	25	4	6.1	6.3
2	31	3	16.2	10.3
3	30	4	5.2	6.5
4	25	20	10.8	10.6
5	28	3	8.4	6.7
6	25	3	9.4	26.0
7	30	10	11.6	25.0
*8	30	17	7.7	25.0
*9	30	2	12.6†	30.0
10	24	4	12.7†	9.6‡
11	29	4	6.0	18.0

*One baby received two courses of steroids, †total white cell count, ‡baby developed septicaemia

evidence to suggest that carbamazepine can control seizures when other anticonvulsants have failed.²

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Sir,

We read Dr Choonara's annotation with interest.¹ Despite a thorough search we have been unable to find any reports of hard data on the acceptability of the rectal route for giving drugs to children although much has been written on the subject. In 1986 therefore we asked the mothers of 193 children (mean age 51.7 months) who were attending the general and surgical paediatric clinics at the University Hospital of Wales or Caerphilly District Miners' Hospital for their views on temperature-taking and medication per rectum. Only five of 55 mothers who regularly recorded their children's temperatures used the rectal route. On the other hand, 15% of the mothers had already given drugs rectally, and altogether 75% professed willingness to use the rectal route should this, for example, obviate a convulsion.

We believe that if they were given proper explanations of the benefits and a clear demonstration of how to do it, most mothers would comply as well with giving drugs rectally as with giving them orally.

Reference

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The disability of short stature

Sir,

The degree of psychosocial adjustment that has to be made in adult life by patients with growth hormone deficiency has been poorly studied. In a recent paper,¹ we reported our experience in the study of the marital, social, and vocational state of 75 short adults (mean age 28 years, 59 men, 16 women) who had been admitted to our clinics

between 1963 and 1980. They had all received long term growth hormone replacement, and 56 patients had presented with multiple pituitary defects that were corrected as appropriate. The final mean (SD) height of the men was 153.5 (3.0) cm and of the women 147.0 (4.0) cm.

Among employable patients (over the age of 21) we found a high (43%) percentage were unemployed or in part time work. The rate of employment was significantly lower than that of their parents or siblings, and of the general population. The distribution of the employed subjects in occupational categories was similar to that of the general population.

Among patients over the age of 21, only 2% were married, and 84% lived with their parents or relatives, confirming the supposition of prolonged economical dependency on the family. Subjects who were working also lived with their families, further illustrating the social isolation of these patients. Similar findings have been reported by Dean *et al* in Canadian adults with growth hormone deficiency.²

A small percentage of the entire group were living in voluntary communities. This tendency to avoid or limit social integration was also confirmed by their preference for single sporting activities that avoid team work.

Surprisingly, scholastic achievement was similar to those of their parents, or siblings, and to that of the general population. In our sample, 5% were university students or had already completed their university studies, compared with 4% of those reported by Dean *et al*² and 32% reported by Galatzer *et al*.³ No difference in the social outcome was observed between men and women or between patients with isolated growth hormone deficiency and those with multiple hypophysiotropic defects.

In conclusion, our results emphasise still further the need to develop and ameliorate the psychosocial support in the routine long term treatment of hypopituitarism. This aspect must be carefully considered in view of the future unlimited supply of biosynthetic growth hormone products.

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SAGM blood

Sir,

In reply to the letter by Robertson and Chiswick,¹ doctors in Sweden probably have the most experience of using SAGM blood. If it is to be used for exchange transfusion they recommend storage for less than five days followed by centrifugation and replacement of the supernatant with frozen AB serum. When reconstituted this provides about 4–5 mg/kg body weight of adenine in each exchange transfusion. They have reported excellent results in neonates. For 'top up' transfusions they use red cells in SAGM, estimating that 10 ml will supply 0.57 mg/kg body weight of adenine. Thus they consider a safe concentration that will be metabolised between transfusions. They have no evidence of complications associated with mannitol (C F Hogman, personal communication).

Dr N Luban presented the results of some cases at a workshop on paediatric transfusion organised by the American Association of Blood Banks in 1985, and described crystals found at necropsy in the kidneys of two babies who had received citrate phosphate dextrose adenine blood. Whether these crystals were in fact 2,8-dihydroxyadenine and whether they had caused any renal damage was not clear.

Kreuger² suggested that the kinetics of adenine metabolism are safe if citrate phosphate dextrose adenine blood is used for exchange transfusions. Despite the lack of evidence to suggest that SAGM blood may cause problems in neonates, we continue to use citrate phosphate dextrose as the anticoagulant in our practice.

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Glycosylated haemoglobin in cystic fibrosis

Sir,

In their letter Caiger *et al* reported on glycosylated haemoglobin concentrations in children with cystic fibrosis.¹ They concluded that this measurement could be of value in the early detection and treatment of associated diabetes mellitus in such patients. Bistrizter *et al*,² however, reported significantly higher glycosylated haemoglobin concentrations in children with cystic fibrosis than in control subjects even in the absence of documented

glucose intolerance. Most of these children were on long term antibiotic treatment.

We would like to draw attention to the interference in glycosylated haemoglobin estimations by penicilloylated haemoglobin. We became aware of this interference when we measured the extent of haemoglobin glycosylation both indirectly by chromatography as haemoglobin A₁ and specifically by the thiobarbituric acid method in children with cystic fibrosis (Fluckiger R, Mathews W, unpublished observations, presented at US National Institute of Health Conference 'Biological mechanisms in aging', June 1980).

The mean glycosylated haemoglobin concentration in children with cystic fibrosis but without diabetes was 9% compared with 7% in control subjects. In contrast, thiobarbituric acid values converted for comparison to glycosylated haemoglobin equivalents were 8% in children with cystic fibrosis and 7% in controls. The usual association between these two indices of haemoglobin glycosylation was apparent from the data for children with cystic fibrosis and overt diabetes but not for those without glucose intolerance (figure). Examination of the clinical records of the children with raised glycosylated haemoglobin concentrations and normal thiobarbituric acid values showed that these children had all been receiving long term treatment with high doses of beta lactam antibiotics. In vitro incubation of haemoglobin with beta lactams leads to covalent attachment of the penicilloyl moiety to haemoglobin and causes glycosylated haemoglobin mobility of the respective haemoglobins. Direct identification of the penicilloyl moiety in the glycosylated haemoglobin fraction from children with cystic fibrosis was unsuccessful because of the small amounts of penicilloylated haemoglobin.

We conclude that glycosylated haemoglobin measurements can be misleading in children with cystic fibrosis receiving treatment with penicillin. In these patients determination of haemoglobin glycosylation by specific

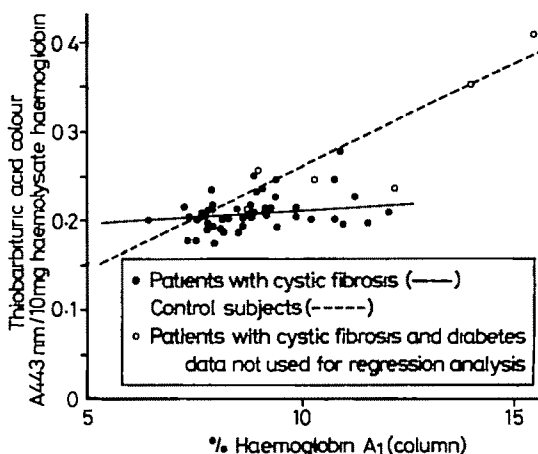


Figure Glycosylated haemoglobin measured by chromatography and by thiobarbituric acid method in patients with cystic fibrosis and controls.

techniques such as the thiobarbituric acid method or boronate affinity chromatography is indicated.

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R FLUCKIGER

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Rotavirus encephalitis

Sir,

Ushijima *et al* describe rotavirus encephalitis¹ and benign convulsions in children with rotaviral gastroenteritis.² We report briefly a further case of probable rotavirus encephalitis.

A boy of 20 months was admitted with a two day history of profuse watery diarrhoea. Admission was precipitated by a tonic clonic fit lasting about 10 minutes. There was no other history of fits in the child or his family, and his psychomotor development had been normal. A second fit occurred at the referring hospital and he had two further fits within 24 hours of admission to the infectious disease unit. He never became feverish.

On examination he was not feverish and fully conscious. Examination of cerebrospinal fluid was entirely normal, plasma concentrations were sodium 135 mmol/l, potassium 4.4 mmol/l, chloride 95 mmol/l, bicarbonate 19 mmol/l, urea 4.6 mmol/l, glucose 5 mmol/l, calcium 2.21 mmol/l, phosphate 1.31 mmol/l, and haemoglobin 124 g/l; the white cell count was $10.1 \times 10^9/l$. Chest and skull x ray pictures, and computed tomogram of the brain were all normal. Cultures of urine and blood were sterile. No pathogens were cultured from swabs of the throat or nose, and no virus was detected in cerebrospinal fluid, urine, or swabs from the throat and nose. Paired serum samples showed no evidence of recent infection with rubella, mumps, herpes hominis, varicella zoster or measles virus, nor with influenza virus A or B, adenovirus, chlamydia, *Clostridium burnetii*, or *Mycoplasma pneumoniae*. An enzyme immunoassay showed rotavirus in the faeces but no rotavirus antibody was detected in the cerebrospinal fluid.

The first electroencephalogram showed a general excess of slow activity most marked in the left temporal region and suggestive of encephalitis. Follow up studies showed gradual improvement with return to normal rhythms four months after admission. During this time his behaviour was aggressive and disruptive, but this settled as the results of the electroencephalograms improved. He continues to develop normally at the time of writing.

The patient was treated with intravenous acyclovir for five days and phenobarbitone. Anticonvulsant treatment was discontinued at the onset of the behavioural abnormalities which did not improve. In retrospect it seems our

patient had benign convulsions associated with rotavirus encephalitis but without specific antibody in the cerebrospinal fluid, as described by Ushijima *et al*.²

I thank Dr J Stevenson for permission to report this case and the Regional Virus Laboratory, East Birmingham Hospital for the ELISA for rotavirus antibody.

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Noonan's syndrome and neurofibromatosis

Sir,

In the February 1987 issue Shuper *et al* described a 12 year old boy alleged to be suffering from Noonan's syndrome and neurofibromatosis.¹ There seems little doubt that their patient had Noonan's syndrome but the evidence for coexisting neurofibromatosis is based solely on the presence of 20 or more café au lait spots, 10 of which we are told were, at the time of writing, over 1.5 cm in diameter.

In the introduction these authors state, 'Multiple café au lait spots are regarded as pathognomonic of von Recklinghausen's neurofibromatosis and have not been reported with Noonan's syndrome.' (my italics). In support of this statement, which is incorrect, they quote a paper by Mendez *et al*.² Dr Mendez, however, in the same issue of the American Journal of Medical Genetics (July 1985) wrote a review article in which she stated '... Noonan's syndrome individuals frequently have multiple pigmented moles, café au lait spots and other pigmentary dysplasias'.³ Furthermore, in two other articles in the same issue of the journal, it is made abundantly clear that café au lait spots are a common finding in Noonan's syndrome alone.^{4,5} Dr Mendez tells me (personal communication) that in her experience in Brazil at least 10% of patients with Noonan's syndrome have café au lait spots.

The Israeli boy reported by Shuper *et al* should, therefore, have been regarded at that stage as having Noonan's syndrome. As he was, however, clearly prepubertal at the time of writing, it is still possible that he may develop (perhaps in late adolescence or early adulthood) neurofibromata or indeed other manifestations of the peripheral form of von Recklinghausen's neurofibromatosis that would then permit a diagnosis of neurofibromatosis Noonan's syndrome, a recently described and rare concurrence.^{6,7}

Authors commenting on café au lait spots in Noonan's syndrome tend not to give details of the size of the cutaneous lesions in their case reports. In future it would

seem desirable for information to be given about the dimensions of these multiple pigmented areas

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Selective examinations on starting school

Sir,

I would strongly agree with the call by O'Callaghan and Colver to abolish the routine medical examination at school entry.¹ They describe a system of selective examination and provide some documentation about the process and about findings. Of course to prove conclusively that such a system is better than routinely examining every child at school entry would require a prospective study of some magnitude, but there is nevertheless much anecdotal evidence to support the notion that the routine medical examination at school entry is an outmoded concept that is an inefficient use of time and resources.

In Australia, as well as in England, the routine medical examination at school entry has been a longstanding tradition. It is a superficially attractive concept to examine every child at school entry, giving some children a clean bill of health and detecting problems in others that can be appropriately treated in order to prevent subsequent sequelae. A more critical analysis of this practice, however, raises a number of issues.²

- (1) It is probable that most important problems have already been detected because most children now have access to a regular source of health care
- (2) It follows therefore that there is a low yield of abnormalities detected at school entry that are both new findings and are important in terms of the child's ongoing health and school performance
- (3) The natural history of some of the conditions detected (for example, serous otitis media) is such that there does not exist an intervention which is widely

accepted and which is known to make a difference to outcome.

(4) Detection of problems does not necessarily result in appropriate treatment or management, because there is usually a reliance on compliance of parents for ongoing referral, etc.

(5) There is overwhelming evidence that important problems at school have to do with the sequelae of chronic illness as well as developmental, behavioural, and psychosocial issues, rather than the sorts of findings detected by a routine physical examination

A recent Australian study concluded that abolishing the school entry examination would allow a 'redistribution of existing resources in order to concentrate more on ensuring effective management of identified problems'.³

There are many methodologies that could be implemented if resources were freed from school entry examinations and applied to the assessment and management of children in need. Callaghan and Colver have described one that obviously works in their school district, and it is inevitable that the needs of school children are better served by such a system than by routine examinations. The authors also argue against routine neurodevelopment examinations at school entry—I would concur strongly with this as well.⁴ It would seem a more productive use of time to confine such detailed assessments to the small group of children who present with difficulties of learning or behaviour rather than to administer such examinations routinely

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Enuresis in children

Sir,

The personal account of enuresis by a 16 year old girl¹ is a reminder that many areas in the United Kingdom lack special facilities for dealing with this common and distressing condition.² Management of enuresis requires specific treatment for the symptom and also help for family difficulties,³ which were evidently present here

Most children with wetting problems have a poor self image, which needs to be bolstered. If a child is referred for diurnal enuresis I ask the head teacher if someone will take him or her regularly to the toilet in a friendly discreet way. The mother is asked to do the same at home. With

older children this is combined with bladder training exercises. Involvement of school staff leads to a supportive atmosphere and, with girls in particular, classmates of their own accord often become helpers too. Most children do well but, if not, urological abnormality or emotional disorder needs to be considered.

In the case of bed wetting, 10–20% of children respond completely to simple supportive measures directed towards relieving them of their fear of waking up wet.⁴ For those that do not respond use of an enuresis alarm is the most effective treatment. It need cause no emotional trauma, and it arrests bed wetting in over 80% of cases.³ Proper supervision is, however, essential; regular clinic visits give opportunities for counselling and for involving the social services, if necessary. The ready availability of psychiatric advice is indispensable in view of the incidence of emotional difficulties in children with enuresis.

Cure of this girl's enuresis may not have been easy, but I believe that much of her unhappiness could have been avoided by wiser management and by advice to her teachers.

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A 'new' manoeuvre for removing foreign bodies from the nose

Sir,

I was impressed by the simplicity of a manoeuvre,

described by Guazzo,¹ for the removal of foreign bodies in the nose, and I was determined to attempt the procedure when the opportunity next arose. Only weeks after I had read the letter my 3 year old daughter dutifully obliged by inserting a plastic bead deep into her nostril.

The method is as follows: an explanation of the procedure is given to the child, age permitting. The patient's unobstructed nostril is gently closed with finger pressure, a gauze swab is applied to the doctor's mouth, which is then opposed to that of the patient. The doctor exhales through the patient's mouth until resistance is felt—this is the epiglottis closing. Once this resistance has been perceived the doctor exhales briskly, providing outward air pressure, this moves the foreign body towards the exterior where it can be easily grasped with forceps. Often the foreign body will actually fly out unaided. The nostrils should be examined afterwards to determine that no further foreign bodies remain and the parent instructed to return should a bloody or offensive nasal discharge develop.

Since deciding to attempt the manoeuvre I have treated several patients. In each case the foreign body was removed in its entirety, with no evidence of trauma on examination of the nares afterwards, and with no further complications.

The biggest advantage of the manoeuvre is that practically no instrumentation is required. This avoids iatrogenic trauma, and especially in the hands of the inexperienced, the problem of inadvertently pushing the foreign body deeper into the nostril on attempted removal.

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Book reviews

The Cerebral Palsies of Children. By Sir William Osler. (*Classics in Developmental Medicine No 1*). Pp 92. £10 hardback. MacKeith Press, 1987. ISBN 0-632-01785-6

One of the fascinations of cerebral palsy is that it engaged the interest of two of the great names of medicine—William Osler and Sigmund Freud. Osler's monograph, based on a series of lectures given in Philadelphia in 1888, was therefore an obvious choice for the first of a series of *Classics in Developmental Medicine*. It is a carefully produced slim volume, which anyone with an interest in cerebral palsy or medical history will want to own. It would be a welcome Christmas present to any paediatric neurologist.

Whether the recipient will simply treasure the book or actually study and learn from it is another matter. It is not an altogether easy read. A large amount of the text is taken up by around 100 brief case reports, written in staccato note style, and reading a dozen or so of these in succession may leave the reader more amused than enlightened. There is also the problem of the classification of cerebral palsy that has bedevilled the subject for over 100 years. Osler's terminology may not be familiar to the modern reader, and some familiar terms are used in a different sense.

Essentially the book is a report on 151 cases. Eleven are labelled 'spastic paraplegia', and probably had what we would call spastic diplegia, with minimal involvement of the upper limbs. Twenty had 'double spastic hemiplegia'. Some of these would now be called spastic quadriplegia, some spastic diplegia, while three evidently had horeoathetoid cerebral palsy. The remaining 120 children had 'infantile hemiplegia'. A few of these were congenital, but the majority had their onset in infancy or childhood, often with fever and convulsions, and often following an acute childhood infection. Thus well over half of the total series had a postnatally acquired disorder, and the case mix is clearly very different from that of present day studies.

The reader therefore needs to be aware that this is not a systematic and comprehensive account of cerebral palsy as it was understood towards the end of the nineteenth century (which Freud's 1897

monograph certainly was), but a set of case presentations of cases rather different from those seen today. In places the perceptive observations of a great clinician shine out—for example, that in hemiplegia the arm is always functionally more affected than the leg, that the younger the child is at the onset of acute hemiplegia the worse is the outlook, and that aphasia in children recovers better than it does in adults.

Other statements and recommendations have not worn so well—like a comment on a child's development which simply notes 'decidedly idiotic', or the recommended management of acute hemiplegia, fever and fits with 'bromides with chloral, a calomel purge, cold to the head, and, if necessary, leeches.' The advice that 'flannel underclothing should be used. Attention to this apparently minor point should be impressed upon mothers; it is too often neglected' has the unmistakable tone of Sir Faraday Bond in Stevenson's *The Wrong Box* (published, like Osler's monograph, in 1889). But then there is a very modern ring to the following 'In such an accident (acute hemiplegia) following vaccination, the doctor is fortunate indeed if he escapes unjust criticism'.

What a classic of this kind really needs is a strong and informative introduction explaining the state of the subject in Osler's time, and his terminology, and a section of explanatory notes on obscurities in the text, and on the historical figures to whom brief allusions are made—like Seguin, Little and the redoubtable Sarah McNutt. In fact it needs the kind of apparatus criticus that one would expect to find in a *Penguin Classic*. After all, the Trojan War is probably no more recondite to the modern reader than the byways of nineteenth century neurology. Lacking this, the serious student of this monograph would do well first to read Dr Tom Ingram's masterly review of the history of classification of cerebral palsy in Stanley and Alberman's *The epidemiology of the cerebral palsies*—or better still in Ingram's own *Paediatric aspects of cerebral palsy*, if he is lucky enough to lay hands on a copy of that classic. It is now regrettably out of print, and deserves republication—perhaps in this series?

R J ROBINSON

Macintosh, Mushin and Epstein: Physics for the Anaesthetist. Seventh edition revised and rewritten by W W Mushin and P L Jones. Pp 660. £32.50 hardback. Blackwell Scientific Publications, 1987. ISBN 0-632-00944-6

Physics is often taught badly because it is essentially an experimental subject and yet teaching is too often confined to abstract theory. This book provides the neonatologist with practical examples of applied physics which relate to the neonatal intensive care unit. It is ideal for the doctor who wants to know the physical basis of the operation of equipment such as humidifiers, gas valves, factors affecting gas flow in endotracheal tubes and so on. The more obscure parts of the book are for the specialised reader who already has a knowledge of electronics. Large sections of the text are naturally devoted to the physics of anaesthesia and will be of limited value to most readers. It also contains useful advice on safety aspects of electricity, vapours, and explosion hazards. It is a useful reference text for all neonatal intensive care units and is easy to read and understand.

ANIL MEHTA

Lecture Notes on Neonatology. By G M Gandy and N R C Robertson. Pp 363. £8.95 paperback. Blackwell Scientific Publications, 1987. ISBN 0-632-00992-6.

If there was a gap in the market for another neonatal textbook, this book (again from Cambridge) has probably found it. In keeping with the other books in the *Lecture Notes* series, the reader will be between medical student level and senior registrar grade. It is not a handbook for the neonatal senior house officer to consult when the baby 'goes off'. It certainly isn't going to help the senior doctor research the published work on osteopaemia of prematurity. It is between the two, and therefore must have been very difficult to write. Although the standard chapters on perinatal definitions, examination of the newborn, infection, and orthopaedic problems, for example, are all there, the strength of the book comes through where personal feeling

enters the writing. Hence the complications of prematurity are dealt with thoroughly. There are 57 pages on physiology of the newborn and respiratory problems. On the other hand, one finds half a page on dwarfs, and four on skin problems—with no pictures. One could say that the book is comprehensive but it is aimed at those who spend much of their lives stuck in special care units. One useful table concerning organisation was what to do when the mother has measles, chicken pox, mumps,

hepatitis, and so on. This was very clear as were all the diagrams, algorithms, and tables.

To make this sort of book readable and different from others one has to have style and dogma. This has come through with predictable clarity and no doubt the book will be held as gospel by the neonatal sen or house officers, while parts will bring smiles to the faces of those already active in the field. When I find a 100 chest drains on routine suction at 10–15 cm H₂O and

patients with meningitis being given third generation cephalosporins that have revolutionised the treatment of this condition I will know the source of these suggestions.

Nevertheless, strongly worded opinions—contentious or not—are attractive to the reader and the book will be a success. Its place will be in the neonatal unit, to be read mainly by nurses, senior house officer and registrars.

J G BISSENDI

British paediatrics

The British Paediatric Association: 60 years

As part of its Diamond Jubilee celebrations the British Paediatric Association (BPA) will commemorate the 60th anniversary of its first annual scientific meeting later this year. The founders of the BPA led by George Frederic Still and Donald Paterson decided that the inaugural meeting should be in some peaceful place in the country away from cities and hospitals. After some debate they chose the Old England Lake Hotel, Windermere as the venue and on 4 May 1928 Still, the first president, and 45 of the 61 founder members of the Association, the *crème de la crème* of British paediatrics, gathered together in the pastoral tranquility of the Lake District not only to discuss scientific subjects but also 'to promote friendship among paediatricians.'

The programme for the meeting is reproduced here. The list of speakers reads like a paediatric roll of honour and many of their names are still remembered with respect and esteem. No less than 14 of them were to become presidents of the Association.

Still was the most eminent of them all. His name is perpetuated in the eponymous title of the disease that he described in his Cambridge MD thesis, *A form of arthritis occurring in children*. He received many honours in his time including the first KCVO to be awarded to a paediatrician. Paterson was the chief architect to the BPA and its first honorary secretary. In 1947 he gave up his posts at Westminster Hospital and Great Ormond Street to return to his native Canada and was appointed professor of paediatrics in Vancouver.

Capon, Spence, Parsons, and Naish were to become professors of child health in Liverpool, Newcastle, Birmingham, and Sheffield. Smellie succeeded Parsons in Birmingham and Neale, the

only guest at the meeting, became professor in Bristol. Spence was the originator of the famous Newcastle 'Thousand Families Survey' and was responsible for starting the practice of admitting mothers to hospital with their children.

Maitland-Jones was paediatrician to the London Hospital and together with Parsons established the Diploma of Child Health for the Conjoint Board in England. Hector Cameron was head of the children's department at Guy's Hospital. The title of his paper gives an indication of his special interest; he was a pioneer of the child guidance movement and his book, *The Nervous Child*, was a seminal work. Pritchard was director of the Infants' Hospital, Vincent Square, London (Westminster Children's Hospital) and played an important part in developing infant welfare clinics.

Schlesinger had been qualified for only five years at the time of the meeting and must have been the youngest member present. He died only a few years ago and his erudition, charm, and humour are still fresh in the memory of paediatricians.

Windermere proved to be a highly popular venue for the annual meeting, largely perhaps for social reasons (and the green fees of 3/6), and the BPA continued to hold its annual meetings there almost without a break for the next 30 years. By 1959, however, the size of the membership and the demands of the scientific programme forced the Association to take its leave of Windermere and transfer the annual meeting first to Scarborough and later to York University, where in 1987 over 1000 members and guests attended. One suspects that those founder members of the BPA who attended the first meeting would not have found such a change to their liking.

A D M JACKSON

This Agenda should be kept and brought to the Meeting.

BRITISH PÆDIATRIC ASSOCIATION.

The first Meeting of the Association will take place at the Old England Lake Hotel, Windermere on May 4th and 5th, 1928.

AGENDA.

Friday, May 4th

- 9.45 a.m. Meeting of the Executive Committee.
 10.0 a.m. General Meeting for the purposes of:—
 1. The election of Officers and Members of the Executive Committee.
 2. The selection of the next place of meeting.
 3. Scientific Business.

10.30 a.m. to
 1.0 p.m.

Morning Session.

COMMUNICATIONS

- | | |
|------------------------|---|
| Dr. Geoffrey Bourne. | "An attack of acute osteitis in a case of Gaucher's disease." |
| Dr. A. Maitland-Jones. | "Pachymeningitis Haemorrhagica of Infants." |
| Dr. Norman Capon. | "Haemorrhagic diathesis in the newborn." |
| Professor F. Langread. | "A case of intracranial Haemorrhage in a child due to congenital miliary aneurysms." |
| Dr. H. T. Ashby. | "Ergot poisoning among children." |
| Dr. C. P. Lapage | "Delay at the pylorus in older children" |
| Dr. J. M. Smellie | "The value of irradiated milk in the treatment of debilitated children of school age" |
| Dr. J. S. Y. Rogers. | "Duodenal ulcer in two successive infants in the same family." |

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7.0 p.m. Association Dinner.

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The British Paediatric Association, coupled with the name of the President. By Dr. Hector Cameron

Reply by the President.

8.30 p.m. to
 10.0 p.m.

Evening Session.

COMMUNICATIONS.

- | | |
|-----------------------|---|
| Dr. Dingwall Forster. | "Corporal punishment in schools" |
| Dr. Hector Cameron. | "Imperative impulses and obsessions in childhood." |
| Dr. Nabarro. | "Modern methods of control of infectious diseases." |
| Dr. K. D. Wilkinson. | "The results of tonsillectomy in rheumatic children in lessening the incidence of cardiac disease." |
| Dr. Schlesinger. | "The incubation period of rheumatic fever." |
| Dr. A. E. Naish. | "Lung consolidation in association with rheumatic carditis." |

Saturday, May 5th.

Final Session.

10.0 a.m. to
 1.0 p.m.

COMMUNICATIONS.

- | | |
|--|---|
| Dr. J. C. Spence. | "Epituberculosis." |
| Dr. Donald Paterson. | "Mediastinal Tuberculosis." |
| Dr. L. G. Parsons with
Dr. A. V. Neale. | "The pathology of coeliac disease." |
| Dr. E. Bellingham Smith. | "Insulin in two cases of coeliac disease." |
| Dr. K. D. Wilkinson. | "Electrocardiographic changes in the hearts of children with diphtheria." |
| Dr. Edmund Cattley. | "Some Remarks on cases of paroxysmal apnoea and dyspnoea." |
| Dr. Hugh Thursfield. | "Myelocytic leukaemia and error in diagnosis." |
| Dr. Eric Pritchard. | "The treatment of hydrocephalus" |
| Dr. R. C. Jewsbury. | "The protein requirements of infants." |

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Annotations

Clinical trials, statistics, and dilemmas

A number of journals over the last decade have drawn attention to faults in the design and statistical analysis of published clinical trials.¹⁻⁵ Research workers may have splendid ideas for evaluating treatments but too often embark on studies with little knowledge of the discipline of good design and very little understanding of the concepts behind the mathematics of statistical analysis. In order to educate the profession in these matters the *Journal of Pediatrics* has introduced 'occasional critiques' of published papers to identify strengths and weaknesses of design and analysis.⁶ Reviews by Schwartz and colleagues,⁷ Gore and Altman,⁸ and Pocock⁹ are accessible to those with little knowledge of mathematics, and the *British Medical Journal's* statistical guidelines for contributors to medical journals¹⁰ should help the novice research worker plan his study to avoid, as far as possible, the many pitfalls he might otherwise encounter. Clinical trials whose results are inconclusive because of poor planning are wasteful of time and resources and their ethics are questionable.

Why are clinical trials important?

The proper evaluation of treatment should avoid anecdote as a way of promoting or condemning a certain treatment. Anecdote is anathema to critical appraisal because it does not remove bias. 'I have seen a number of patients whose symptoms have improved by treatment X. They will vouch for it.' This line of thinking is still widely prevalent and when such testimonials are presented, whether at academic meetings or in the media, they should be challenged. The statement would be better put 'I have formed the clinical impression that . . . Could it be important and worth validating? Is it real or is it artefactual? I must attempt to answer these questions objectively.'

'SUCCESS' STORIES

If, for example, it was publicised that a treatment for AIDS had produced a 'fantastic' improvement in three or four patients in whom it had been tried, it would be understandably very difficult to enrol patients for a clinical trial to evaluate such treatment. Some of the worst examples of this kind of

promotion are the world wide 'treatments' available for cerebral palsy. Families who have heard of their 'success' may pay huge sums of money to have their child treated. Even when a treatment that has been publicised to be of possible value has been subsequently shown to be worthless, it can still be very difficult to convince both patients and doctors that this is so. The Third World countries, for example, continue to pay huge sums for valueless antidiarrhoeal preparations.¹¹

NON-VALIDATED TREATMENTS ALREADY IN PRACTICE

Once treatments have become part of standard practice without proper validation it can become extremely difficult to test them. What exactly is the place of physiotherapy in the management of cerebral palsy? For which patients is psychotherapy useful? If a treatment is 'safe' then why not use it just in case it may be valuable? Such examples of treatments have been chosen because at first sight both may be considered harmless and thereby accorded the 'benefit of the doubt.' Both, however, are time consuming and costly with potential effects on the rest of the family. Hopes may be raised without justification. As it would be very difficult to enrol patients for randomised controlled trials of these treatments versus no treatment, other methods, such as standard treatment against a less intensive variation of treatment, would have to be devised.

Patients, especially those with lethal or chronically disabling disorders, are a very vulnerable group. It could be argued that the offering of treatment which has not been validated or shown, in the widest context, to be harmless is a form of exploitation. This is of course a contentious issue and deserves continuing debate. It may be that for society as a whole just 'doing something', whether of proven value or not, is good enough reason to continue certain treatments that are particularly difficult to evaluate.

ASSOCIATION AND CAUSE

Some treatments are particularly difficult to validate. The management of patients with cystic fibrosis at specialist centres has been shown to be associated with improved mortality rates.¹² Associa-

tion is not cause but it is easy to argue that in this case it seems reasonable to conclude that the association is causal. It may indeed be reasonable but nevertheless untrue! It should be made very clear that when policy decisions are made on the basis of such associations they are based only on conjecture. Unwanted effects of treatment may also be difficult to evaluate. The nature of the relationship between oxygen treatment and the retinopathy of prematurity has not been, and may never be, defined.¹³ Yet the conviction, based on circumstantial evidence, of the causal nature of the association has influenced both medical and legal opinion for the last three decades.

Randomised controlled clinical trials

In 1773 when Dr Johnson considered why population numbers may have been exaggerated in the past he remarked: 'To count is a modern practice, the ancient method was to guess; and when numbers are guessed they are always magnified.'¹⁴ An analogy to this could be made in respect of clinical trials: controlled studies remove bias; uncontrolled studies exaggerate the value of a new treatment, often grossly. As accurate counts must have been difficult in Johnson's day, the conducting of a controlled clinical trial 'to remove bias' is far from easy in the present day.

PATIENT SELECTION AND INFORMED CONSENT

Dudley has recently drawn attention to a trial where difficulties in patient selection have cast doubt on the result of a time consuming and no doubt costly study.¹⁵ When patients are invited to participate in a trial of a new treatment where, at the toss of a coin, they may be allotted either the new treatment or an old or no treatment, some refuse to participate and select the treatment they prefer. This is one of the problems encountered when informed consent to enter a study is necessary. For example, if a comparison of home and hospital management of a behavioural problem were to be undertaken many families might not wish to take the chance of their child being randomised to a particular group. The behavioural patterns of the participants and the non-participants may well be different. How to deal with those who elect not to enter must be considered at the planning stage. The outcome of all patients who present with entry requirements must be included in the report.

TRIAL SIZE, CLINICAL SIGNIFICANCE, AND STATISTICAL SIGNIFICANCE

Another problem that must be considered at the design stage is the size of the trial—that is, how

many patients must be enrolled in order to detect reliably whether or not a new treatment is useful. To estimate this the smallest clinical change worth demonstrating should be decided. For example to demonstrate that a new treatment would reduce the admission rate for gastroenteritis by 25% might be worthwhile, whereas to demonstrate with statistical significance that it made a reduction of 5% might be considered not worthwhile. The number of patients required for a trial is inversely proportional to the square of the size of change considered clinically important to identify. Another question often asked by drug companies is whether a new drug is as good as one already marketed. If the new drug is cheaper or is thought to have fewer side effects, how much less effective would it have to be to make it an unacceptable alternative? The number of patients enrolled for the trial would have to be sufficient to demonstrate reliably whether or not this difference existed. If the clinical change is to be measured by a quantitative method, such as change in peak expiratory flow rate or the concentration of a serum constituent, then the variability of the measurement in the population—that is, its standard deviation—should also be known. Using this information together with figures for the risk of a false positive result—that is, the Type I error, usually 5% but preferably 1%—and for the risk of a false negative result—that is, the Type II error, usually between 5 and 20%—the number of patients to be enrolled for the study can be calculated.⁹ It is when insufficient attention has been paid to the exclusion of large Type II errors that the problem of 'negative' studies arises. Many studies which have reported 'no significant differences' between two treatments have simply not been powerful enough to show a difference, which may well have existed. Such studies have presented inconclusive results because of failure to enrol enough patients. An excellent commentary on this problem together with a worked example has recently been presented by O'Brian Smith.¹⁶

What size of change would be important to demonstrate may be difficult to decide. Another difficulty may be accruing sufficient numbers. The study of preventive measures and treatment for the retinopathy of prematurity, for example, would require the enrolment of patients from several centres. If the desired trial size is too large then it is better abandoned before it starts.

MODELS AND PILOT STUDIES

It is worth while to set out on paper during the planning stage possible series of results and then to analyse them as if for presentation including statistical analyses. This is a good way of developing a

'feel' for the variability in response and size of the trial and also a good exercise for understanding the concepts behind the statistics. Plans at this stage can be made for the timing of interim analysis, if this might be necessary.

If there is anxiety about accrual of patients, which may be particularly difficult when informed consent is necessary, a pilot study should be undertaken. This also gives an opportunity to examine the logistics of data collection, clarity of questionnaires, and so on. Apart from these concerns the period of the pilot study allows time for 'thought clarification', which may well have a good positive effect on a study protocol.

STATISTICAL CONSIDERATIONS

The *British Medical Journal* has led the way in this country in laying down guidelines for the analysis of clinical trials.¹⁰ The researcher should become familiar with presenting his results using confidence intervals when appropriate as these emphasise the clinical importance of results more than the statistical importance.¹⁷ (Observations which require non-parametric analysis do not, however, lend themselves easily to this.) Other useful concepts to understand are the proper collection and handling of ordinal data^{18 19} and the organisation of a crossover study.^{8 20}

Presentation of results

Good presentation is good communication. Apart from this, presenting the reader (and referee!) with all the data allows him to evaluate the analyses that were carried out for himself. Guidelines for the best ways of doing this diagrammatically are easily available.^{8 21}

Responsibilities

Clearly the investigator and his supervisor have responsibilities to familiarise themselves with the requirements of good study design. It is a waste of both investigators' and patients' time if every effort has not been made to ensure that a trial is likely to give a conclusive result. Ethical committees, among other considerations, must be aware of the importance of good study design and assure themselves of the scientific validity of any proposal.²² If no member of the committee is able to properly evaluate this, the committee should consider sending the proposal for consultation.

Editors of journals and referees of papers submitted for publication and presentation at academic meetings bear a great responsibility for criticising work of poor design and statistical validity. The use of a check list may be worth while.²³ The statistical

considerations for a trial including calculations for the number of patients to be enrolled should be clearly laid out in the methodology section. Referees should encourage authors to present, in a suitable form, their raw data, as far as is possible.

Conclusion

One of the ethical considerations of clinical research is its scientific validity. This needs to be considered, and seen to have been considered, at the planning stage of any clinical trial. It is the business of investigators, supervisors, ethical committees, referees of papers and editors of journals to ensure that, as far as possible, trials are conducted which have the greatest chance of reaching a conclusive result. Time and resources are otherwise wasted and the only beneficiary is the investigator who may have learnt from his mistakes. Policy decisions may sometimes have to be made based on information from retrospective and uncontrolled studies and when this is done it should be made clear that they are based on conjecture only; the risk of hampering further research must be considered and acknowledged.

I am grateful to Professors Dudley and Simpson and to Dr Carol Devaux for helpful comments on a first draft.

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The doctor's role in the prevention of accidents

It has been said elsewhere that doctors working in the field of child health should be more aware than they appear to be at present of the part that they can play in preventing accidents—which are the most important problem in the health of children after the first year of life. Yet many doctors do not know what they can do in this field; this paper is an attempt to detail the different approaches that might be made by doctors in the various branches of the health services for children.

Two general aspects of accident prevention work need to be stated here. First, that almost all of it involves liaison with other professions or disciplines. This is in contrast with most other paediatric preventive work—for example, immunisations—where the responsibility lies almost entirely within the province of the health services and which is carried out by health workers. But it is obvious that the prevention of road accidents, for example, involves many disciplines other than health, and therefore doctors must be prepared to work in close collaboration with others. The second general point is that an accident or injury involves a child coming into contact with a harmful 'agent' under a defined set of circumstances—physical, psychological, and social. Accident prevention work can therefore be directed towards one or more of these areas: education of the child or of those responsible for him, a reduction in the potential for harm of the 'agent', and a change in the environmental circumstances under which the accident or injury took place. A useful general question to ask oneself is 'As this particular child was injured by this particular object in this particular way under this set of circumstances, how can I prevent another child being injured in the same way and under the same circumstances?'

Paediatricians and other child health doctors are in direct contact with the child and his parent and therefore much of the emphasis of the role of doctors actually dealing with the injured child will be epidemiological and factual: in finding out the details of the factors involved and in passing on this information to others who may be in a position to take preventive action. Other doctors—for example, clinical medical officers and general practitioners, who may not see the child at the actual time of the injury, may find that their work is more educational either by direct discussion with mothers in clinics or surgeries or by encouraging health

visitors in accident prevention work. Health visitors have a prime role in this whole field and their function has been the subject of a special study and report by Ms Pam Laidman of the Child Accident Prevention Trust¹ and will therefore not be discussed further here.

More detailed suggestions of the parts that might be played by specific doctors are now given.

Community paediatricians

The role of the community paediatrician should primarily be to study the epidemiology of accidents in his area: how many and of what type, how and where they occur and to whom. Information on these aspects is essential if a local accident prevention campaign is to be mounted: not only do local problems need to be identified to make the campaign as relevant as possible, but the continued collection of data is needed to monitor the effectiveness of the campaign.

Collection of satisfactory data will not necessarily be easy, as most accident and emergency departments do not collect the type of information that is really needed for accident prevention work, and the community physicians first task may well be to improve the data collection system. It must be

Table *Organisations or people who may collect data at a local level on accidents to children*

Health aspects
Hospital inpatient enquiry
Hospital activity analysis
Accident and emergency department
General practitioner
Road accidents
Police
Road safety officer
Highway or engineers department
Home accidents
Home accident surveillance system
Home safety officer
Trading standards officer
Others
Environmental health officer
Education authority
Health and safety executive
Recreation and leisure department

remembered too that other disciplines collect data of their own (table). This emphasises the multidisciplinary nature of accident prevention: police, road safety officers, teachers, home safety officers, health education officers, trading standards officers as well as members of the health professions, particularly health visitors, may all be involved at a local level. It may well be that in due course the community paediatrician may call together a local child accident prevention group involving health authority and local authority officials as well as voluntary groups. He would then be able to present information on the size and nature of the problem and in this way he is likely to be the intermediary between the health services and the other agencies involved.

If there is no community paediatrician in the district then this epidemiological and coordinating role is likely to be taken on by the district medical officer in conjunction with the senior medical officer (child health), or whoever is designated as being responsible for the community child health services.

Clinical medical officer (community health doctors, child health doctors)

The role of the clinical medical officer would seem to be a dual one. Firstly, to take part in the education of mothers either in face to face discussions in the clinic or by talking to parent groups, and to work with the health visitors associated with the clinic. Secondly, to receive information from health visitors and mothers about safety matters—toys or other products considered to be unsafe, road crossings or toddler playgrounds that seem to present an undue hazard. This information can then be passed on to the appropriate local authority or to the person in the health authority concerned by the community paediatrician. Doctors involved with schools should ensure that accidents and their prevention are included in the health education programme of their schools.

General practitioner

Although general practitioners do not come under the administrative wing of the local health authority, they are included here as they are obviously involved in the health care of children. They deal with many minor injuries to children, and, particularly in rural areas, with major injuries too. In dealing with these their role is similar to that of hospital doctors discussed below, but in addition they play a part similar to the clinical medical officers in educating parents. In the course of their

home visits they may be able to point out hazardous practices or features of the house such as dangerous glass doors, bannisters or balcony railings, trailing kettle flexes, etc, and thus they have the potential to be able to reduce home accidents quite considerably. Another example of where the general practitioner can exert his influence is in increasing the use of child safety seats in cars.

Hospital doctor

The joint memorandum on the management of children in accident and emergency departments issued jointly by the British Paediatric Association and the Casualty Surgeon's Association,² suggests that a consultant paediatrician should be designated as having a particular relationship with the accident and emergency department in respect of children attending there, and it would seem sensible for this consultant also to be concerned with aspects relating to accident prevention.

In contrast with the epidemiological role of the community paediatrician the hospital doctor's role will be more concerned with the analysis needed to uncover the causes of the accident. He, his staff, or the doctors in accident and emergency must be prepared to go into detail about the agent and the environmental circumstances of the accident: was the child restrained and in which seat was he sitting in the car accident? Was the child cyclist wearing a cycle helmet? Which particular piece of equipment and in which playground did the child fall from? Was the school playground supervised at the time? Were the mother's tablets that the toddler got hold of in a child resistant container, and if not had the mother taken them out of one or had the pharmacist not dispensed them in a child resistant container—and if not, why not? How did the child manage to climb up the balcony railings before he fell over—were there horizontal bars that he could climb? Was the lollipop lady on duty at the time or was she off sick? What was the make of the high chair that the child managed to unbalance? These and similar questions need to be answered and the information passed either through the community paediatrician or direct to the local authority officer concerned. It can then be collated together with information from other sources so that appropriate preventive action can be taken in respect of consumer product safety, the safety of playground equipment, the placing of road crossings, and in very many other ways.

Conclusion

Only when child health doctors assemble the in-

formation of the accidents and injuries that they deal with and begin to work with other disciplines in the field of prevention will a real impact be made on the reduction in the deaths and injuries to children from accidents.

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See Special report p 318

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Original articles

Ciliary abnormalities in respiratory disease

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SUMMARY One hundred and sixty seven children, ranging in age from 5 weeks to 16 years, with chronic upper or lower respiratory tract problems, or both, were investigated for ciliary dyskinesia. Abnormal ciliary function was found in 18 cases all of whom had chronic lower respiratory disease and most of whom also had upper respiratory problems. Fifteen of the 18 cases had reduced ciliary beat frequencies (<10 Hz) associated with dyskinesia and the other three showed apparent absence of ciliated cells. Of the 15 cases with reduced ciliary beat frequencies, ciliary ultrastructure was normal in seven cases but abnormal with missing dynein arms and occasional abnormalities of microtubular arrangement in eight. Respiratory symptoms in the perinatal period were more common in children with abnormal ciliary function and present in all those with ultrastructural abnormalities or absence of ciliated cells compared with 34 (26%) of 132 children, in whom symptoms were recorded, with normal ciliary function.

This study would suggest that all children with unexplained chronic respiratory disease, in particular those with symptoms starting in the perinatal period, should be investigated for ciliary dyskinesia.

Primary ciliary dyskinesia, or the immotile cilia syndrome, was first described in association with Kartagener's syndrome (situs inversus, bronchiectasis, and sinusitis).¹ The condition is thought to be inherited in an autosomal recessive manner and to affect 1 in 15 000 people.² Impaired ciliary function is thought to result from absence of the dynein arms that are normally attached to the outer microtubular doublets within the cilium (fig 1). Reduced ciliary motility causes reduction in mucociliary clearance and predisposition to infection throughout the respiratory tract. In addition, it is speculated that the abnormality disturbs the normal developmental symmetry of vital organs resulting in random laevo or dextroposition of such organs as the heart, liver, and spleen.¹ Affected males are usually infertile because their sperm, being of similar structure to cilia, are poorly motile or non-motile.

More recently it has become apparent that there is a wider pattern of ciliary abnormalities than was originally recognised. Ultrastructural abnormalities range from the complete absence of dynein arms to partial absence affecting the outer or inner arms only. Microtubules may be rearranged or lost and transposition or duplication anomalies can occur.³ Ciliary ultrastructure may be normal despite im-

paired function as defined by a reduction in ciliary beat frequency,⁴ and there are reports of ciliary aplasia occurring throughout the respiratory tract.^{5,6}

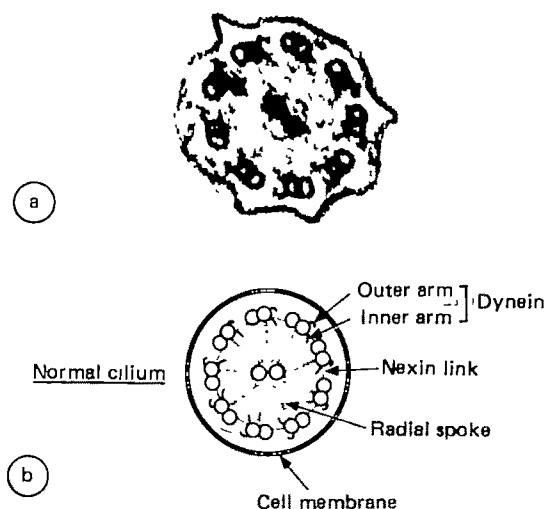


Fig 1 (a) Electron micrograph (magnification $\times 100\,000$) and (b) schematic drawing (courtesy of A Dewar) of transverse section of a normal cilium

In addition, ciliary dyskinesia may be secondary to viral or bacterial infection, returning to normal with appropriate treatment and time.⁷⁻¹⁰ Respiratory problems associated with ciliary dyskinesia are well recognised in childhood, indeed the diagnosis should be considered in any neonate or infant with unexplained respiratory distress.^{11 12}

Since April 1985 it has been our policy to include examination of ciliary function as part of the routine procedure for investigating children with chronic upper and lower respiratory tract disease of unknown aetiology and we report the results of testing 167 children over a 26 month period

Patients and methods

One hundred and sixty seven children (79 girls and 88 boys; age range 5 weeks to 16 years) were studied between April 1985 and May 1987. Most had either recurrent or chronic upper or lower respiratory symptoms, or both, of more than one month's duration. Five asymptomatic siblings of affected children were also investigated. In most cases examination of ciliary function was performed together with other investigations: these included a chest radiograph to determine the cause and extent of lower respiratory tract disease and organ situs.

In vitro examination of ciliary function was performed by a photometric technique¹³ measuring ciliary beat frequency with automated recording.¹⁴ A sample of ciliated epithelium was obtained from the inferior turbinate of the nose using a cytology brush without anaesthesia.¹³ The cilia were suspended in 2 ml of medium 199 cell culture fluid (Flow Laboratories) and a small sample examined in a sealed microscope slide-coverslip chamber. The preparation was placed on an electronically controlled warmstage (Microtec) at 37°C and allowed to equilibrate for several minutes. Providing there were two or more strips of intact ciliated epithelium present measurement of ciliary beat frequency could be performed. If there were fewer than two strips of ciliated epithelium a second nasal brushing was performed. Occasionally epithelial strips were found with disrupted ciliated borders or with absent cilia and associated with the presence of mucopurulent material. In these cases the child was prescribed a course of systemic antibiotic and topical nasal antibiotic with corticosteroid drops and the brushing repeated several weeks later. Ciliary movement was inspected and ciliary beat frequency measured on a Leitz Dialux 20 phase contrast microscope at a magnification of 320. The cilia were positioned to interrupt a passage of light through a small diaphragm into a Leitz MPV compact microscope photometer. This converted light intensity into an

electrical signal that was subsequently read as a ciliary beat frequency in Hz using a ciliary beat frequency processor unit. At least three readings of beat frequency were made on at least two strips of ciliated epithelium and a mean value calculated. Where cilia were present with a mean ciliary beat frequency of less than 10 Hz a second brushing for ultrastructure was performed and the cilia immediately fixed in 2.5% glutaraldehyde in cacodylate buffer and then postfixed in 1% osmium tetroxide. After agar embedding and Araldite infiltration sections were cut and examined by light and transmission electron microscopy.¹⁵

A normal range for ciliary beat frequency in the age range studied has not been obtained (for ethical reasons), but there seems to be no variation with age in normal adults. In our laboratory the ciliary beat frequency in normal adults is usually found to be in the range of 12 to 15 Hz in comparison with subjects with primary ciliary dyskinesia associated with Kartagener's syndrome where the frequency is usually less than 10 Hz.¹⁶ We have therefore considered any ciliary beat frequency of less than 10 Hz to be appreciably abnormal.

Results

Children were referred with a wide range of respiratory problems as listed in table 1. The five asymptomatic children, the near-miss cot death, and the child with obstructive apnoea all had normal ciliary function

Eighteen children were found to have either low ciliary beat frequency with abnormal ciliary ultrastructure (eight cases), low ciliary beat frequency

Table 1 *Main clinical indications for referral (No of children=167)*

Indication	No of cases (%)
Lower respiratory tract problems	
Pneumonia/chest infection	60 (36)
Recurrent/chronic cough	44 (26)
Unexplained wheeze	17 (10)
Lobar collapse	15 (9)
Bronchiectasis	10 (6)
Pulmonary abscess	2 (1)
Bronchopulmonary dysplasia	1 (<1)
Ventilator dependence in the neonate	1 (<1)
Upper respiratory tract problems	
Chronic rhinorrhoea/stuffiness/obstruction	7 (4)
Sinusitis	3 (2)
Other reasons	
Asymptomatic siblings	5 (3)
Obstructive apnoea	1 (<1)
Near-miss cot death	1 (<1)

with normal ultrastructure (seven cases), or apparent absence of ciliated cells (three cases) (table 2). In those with a reduced frequency the cilia appeared dyskinetic with reduced amplitude and abnormal beat patterns. Their clinical features are summarised in table 3. All 18 children had chronic lower respiratory problems and 13 also had upper respiratory symptoms. Nine of 167 children underwent a second nasal ciliary examination after a period of treatment. In three of these ciliated cells were found to be persistently absent from the brushings, in the one case who had a bronchoscopy ciliated cells were also absent from a bronchial mucosal biopsy specimen. In the remaining six children the ciliary beat frequency was normal on the second examination. Four of the children with a low frequency or absence of ciliated cells had situs inversus (one with normal ultrastructure and three with abnormal ultrastructure) and two others had siblings with Kartagener's syndrome. Fourteen were reported by their parents

or referring paediatrician to have had either upper or lower respiratory tract problems in the first week of life. All of the children with ultrastructural abnormalities or absence of ciliated cells were noted to be symptomatic in the first week of life. This may be compared with the children with normal ciliary function where recorded symptoms occurred in only 34 out of 132 (26%) cases during the first week of life. A χ^2 analysis using Yates's correction for small numbers ($\chi^2=22.6$, $n=143$, $p<0.001$) showed this difference was highly significant.

The ultrastructural defects seen on electron microscopy in the eight cases are shown in table 4. All had either absence of inner, outer, or both inner and outer dynein arms. In addition, most also had occasional abnormalities of microtubular arrangement—usually disarrangement of the outer doublets (taking the form of transposition defects) and extra tubules. The following case report is typical of the 18 cases with abnormal ciliary function.

Table 2 *Pattern of ciliary function and ultrastructure in all 167 children investigated*

	No (sex)	Median age (years)	No with symptoms in first week of life	No with situs inversus	No with family history of Kartagener's syndrome
Cilia absent	3 (3 girls)	8.4	3	0	0
Cilia present Ciliary beat frequency <10 Hz Abnormal ultrastructural appearance on electron microscopy	8 (4 girls, 4 boys)	5.2	8	3	2
Cilia present Ciliary beat frequency <10 Hz Normal ultrastructural appearance on electron microscopy	7 (5 girls, 2 boys)	6.3	3	1	0
Cilia present Ciliary beat frequency >10 Hz	149 (67 girls, 82 boys)	4.1	34/132*	7	0
Total	167 (79 girls, 88 boys)	4.1	48/150*	11	2

*Presence of symptoms in first week of life not known or recorded in 17 cases

Table 3 *Clinical features of 18 children with ciliary abnormalities*

Clinical features	Cilia absent (n=3)	Cilia present, ciliary beat frequency <10 Hz abnormal ultrastructural appearance on electron microscopy (n=8)	Cilia present, ciliary beat frequency <10 Hz normal ultrastructural appearance on electron microscopy (n=7)
Chronic cough/chest infections	3	8	7
Chronic rhinorrhoea/stiffness/obstruction	2	6	5
Bronchiectasis/persistent lobar collapse	2	3	1
Situs inversus	0	3	1
Family history of Kartagener's syndrome	0	2	0
Sinusitis	1	1	0
Hearing defect	0	2	0

Table 4 *Predominant ultrastructural defect in the eight cases with abnormal ultrastructure*

Case no	Number and type of dynein arm abnormalities (% cilia counted)	Number and type of microtubular arrangement abnormalities (% cilia counted)
1	37 (86) absent inner 2 (5) both absent	31 (24) outer doublets disarranged 4 (3) outer doublets extra tubules
2	5 (19) absent inner	9 (20) outer doublets disarranged 2 (4) outer doublets extra tubules 2 (4) outer doublets single tubules
3	229 (91) absent outer 11 (4) both absent	24 (4) outer doublets extra tubules 14 (2) outer doublets disarranged
4	66 (75) absent outer	4 (2) outer doublets extra tubules 4 (2) compound cilia
5	11 (52) absent inner	15 (36) outer doublets disarranged 3 (7) central pair missing 2 (5) compound cilia
6	100 (88) both absent 12 (11) absent outer	7 (3) outer doublets extra tubules 7 (3) outer doublets disarranged
7	14 (78) both absent	1 (2) outer doublets disarranged
8	12 (86) both absent 2 (14) absent outer	2 (4) outer doublets extra tubules 1 (2) outer doublets disarranged

Case report

A 6 year old boy (case 4) with a history of chronic productive cough and nasal discharge was referred for investigation. He had been born at full term after a normal delivery and a normal pregnancy and had weighed 3800 g. Nasal stuffiness and discharge were noted from the first day of life and had required treatment with an antibiotic during the first week. From 15 months of age he had required frequent courses of oral antibiotics for chest infections and he failed to thrive. His parents first noted hearing problems when they found that they had to shout in order to draw his attention. An older brother had died at the age of 10 years after cardiac surgery for complex congenital heart disease and situs inversus. He was thought to have had Kartagener's syndrome, but had not undergone ciliary function testing. A younger sister was asymptomatic.

Examination showed a thin boy without finger clubbing. There was appreciable chest deformity (with pectus carinatum and bilateral Harrison's sulci), inspiratory crackles at the left base, purulent nasal discharge, and bilateral serous otitis media. A chest radiograph showed cardiac and abdominal situs solitus and increased shadowing in the left lower lobe. Forced expiratory volume in one second and forced vital capacity were reduced, this suggested a mixed obstructive and restrictive ventilatory defect. An ^{81}Kr ventilation scan indicated reduced ventilation in the anterior, lateral, and posterior basal segments of the left lower lobe and

the medial segment of the right upper lobe. Sweat electrolyte secretion was normal. *Haemophilus influenzae* and *Streptococcus pneumoniae* were cultured from a sputum sample.

Ciliary function was examined in an epithelial brushing of the inferior nasal turbinate. Cilia seemed dyskinetic, moving stiffly and asynchronously with reduced amplitude and had a ciliary beat frequency of less than 10 Hz. Electron microscopy (fig 2) showed outer dynein arms to be absent from

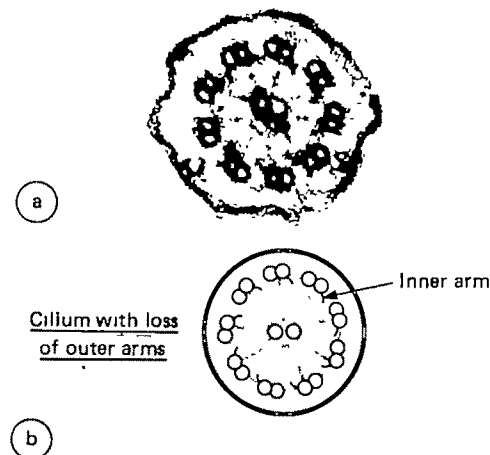


Fig 2 (a) Electron micrograph (magnification $\times 100\,000$) and (b) schematic drawing (courtesy of A Dewar) of transverse section of a cilium from case report showing missing outer dynein arms.

75% of the cilia counted, there were occasional extra tubules adjacent to the outer doublets (2%) and compound cilia (2%). After the diagnosis of primary ciliary dyskinesia he was treated with a course of oral cefaclor for one month and started regular physiotherapy. There was some improvement in his condition notably a reduction of cough and sputum.

Discussion

Including the three cases where no ciliated cells could be found we estimated the prevalence of abnormal ciliary function to be 13 out of 167 cases (11%). In the 145 children where the ciliary beat frequency was greater than 10 Hz the cilia invariably appeared to beat in a normal coordinated pattern.

In Kartagener's syndrome it has been shown that, while the occasional patient may be found with normal ciliary function and ultrastructure, there is a clear relation between the level of reduction in ciliary beat frequency and the number of ultrastructural abnormalities present.¹⁶ Most cases have a frequency below 10 Hz with more than 50% of the dynein arms missing. Tests of ciliary function in adults often include measurement of nasal mucociliary clearance by the saccharin test in which a small particle of saccharin is placed behind the anterior border of the inferior turbinate and the time taken to perceive a sweet taste recorded. This test, however, requires considerable cooperation from the subject and, like others, we have found that the test is not suitable for children under the age of 10 years.³

In a survey of this nature it is not possible to be certain whether the functional and structural ciliary defects seen represent the primary ciliary dyskinesia associated with Kartagener's syndrome or are secondary to the damaging effects of either pathogenic or host factors.⁷⁻¹⁹ It is recognised that infection can cause transient dyskinesia, which is more often associated with microtubular abnormalities than with loss of dynein arms; this may return to normal with appropriate treatment and time.⁷⁻⁹ Nine children were noted to have ciliary dyskinesia or absence of ciliated cells in the presence of mucopurulent material. After treatment six had normal ciliary function but three had persistent absence of ciliated cells. This might still be a secondary phenomenon, although primary failure of ciliogenesis has been reported before and is possibly inherited in an autosomal recessive manner.⁶ It was our observation, however, that many of the children with normal ciliary function had mucopurulent nasal discharges. It is therefore probable that if ciliary function and structure are altered by infective agents

then not all pathogens have this effect. Alternatively, there may be mechanisms operating to protect cilia in those individuals with infection and normal ciliary function that are absent in those with ciliary dyskinesia. The anomalies of microtubular arrangement seen in those with missing dynein arms were infrequent and probably non-specific. Such appearances have occasionally been found in the cilia of normal individuals.¹⁶⁻²⁰ The seven children with abnormal ciliary function but normal ultrastructure depart from the usual pattern of ciliary dyskinesia. This finding has been documented in the past and may represent a metabolic abnormality within the cilia with no morphological counterpart.^{3,4}

Fourteen of the 18 children with abnormal ciliary function, and all the children with abnormal ultrastructure or absence of ciliated cells, had symptoms starting in the perinatal period (table 2). This finding would suggest that any child with chronic lower respiratory disease starting in the perinatal period should be investigated for ciliary dyskinesia. While most of the children with ciliary abnormalities were noted to have upper respiratory problems as well this was not inevitable. It is important to make the diagnosis not only because of its implications regarding later male infertility, but also because more invasive investigations into other possible causes for the respiratory problem may be avoided. In the United Kingdom there are currently only one or two centres with facilities for investigating ciliary function and ultrastructure. This study would suggest that ciliary dyskinesia is not that uncommon in children with unexplained chronic respiratory disease and that wider facilities should be available for investigating suspected cases. Although there is no specific treatment for the condition, supportive management with regular physiotherapy and use of antibiotics may prevent or delay the onset of bronchiectasis.

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Tubular dysfunction and microalbuminuria in insulin dependent diabetes

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SUMMARY The nature of microproteinuria in the early years of insulin-dependent diabetes was investigated in a cross sectional study of 80 children with insulin-dependent diabetes and 40 normal children. Urinary excretion of three low molecular weight proteins: α -1-microglobulin, β -2-microglobulin and κ light chains was used as an index of proximal renal tubular function. The first urine samples of the morning were collected and excretion of proteins measured was expressed as ratio of protein to creatinine. There was a strong correlation between excretion of α -1-microglobulin and κ light chains and their excretion was significantly higher in diabetic children indicating decreased proximal tubular reabsorption. The excretion of β -2-microglobulin was found to be an unsatisfactory index of proximal tubular function. Urinary albumin excretion was not significantly raised in diabetic children and did not correlate with urinary α -1-microglobulin or κ light chain excretion. Glycaemic control might influence proximal tubular function as both urinary glucose concentration and glycosylated haemoglobin showed correlations with urinary α -1-microglobulin excretion and with urinary κ light chain excretion.

Proteinuria results from increased glomerular filtration or impaired tubular reabsorption. Interest in microproteinuria in diabetes mellitus has focused mainly on albumin excretion. The interest was aroused by the finding that in adults with insulin-dependent diabetes (IDDM) microalbuminuria (overnight albumin excretion rate $>30 \mu\text{g}/\text{minute}$) subsequently progressed to persistent proteinuria detectable with Albustix.¹

Excretion of low molecular weight proteins serves as an index of proximal renal tubular function as proteins with molecular weight less than 40 000 are freely filtered by the glomerulus and more than 95% is then reabsorbed and catabolised by the proximal tubule. The view that the microproteinuria of diabetes is solely of glomerular origin is based on observations that β -2-microglobulin, a protein of molecular weight 11 800, is excreted normally.² This is not upheld, however, by the results of analyses using sodium dodecyl sulphate polyacrylamide gel electrophoresis of urinary proteins, which have disclosed patterns consistent with tubular proteinuria.³⁻⁵ Furthermore, Teppa and Groop have reported increased excretion of the κ light chains of immunoglobulin (molecular weight 23 000, dimer 46 000) in adults with IDDM.⁵

Accordingly we decided to investigate proximal renal tubular function in patients with diabetes by measuring excretion of three proteins with low molecular weight: α -1-microglobulin (molecular weight 31 000), β -2-microglobulin, and κ light chains. The study was carried out in children with IDDM so that the confounding variables that are found in many adult diabetics, who are often receiving concomitant drug treatment and where there is the possibility of other diseases, could be excluded. This approach also examined the prospect that the assays might prove sensitive markers of abnormal renal function in diabetes, preceding the appearance of microalbuminuria.

Patients and methods

Eighty children with IDDM (40 boys and 40 girls) seen consecutively at diabetic clinics in Leeds and Huddersfield and a control group of 40 normal children (19 boys and 21 girls) who were not attending hospital and who had no family history of diabetes in a first degree relative, took part in the study. All children were less than 16 years old, with a mean (SD) age of 10.5 (3.5) years for children with IDDM and 9.2 (3.3) years for children in the

control group. The mean (SD) duration of diabetes was 3.8 (2.9) years. None of the children had symptoms of urinary tract infection.

The first urine samples of the morning were collected prospectively from all subjects and stored at -20° with 0.1% sodium azide as preservative. Urinary protein concentrations were measured and expressed as ratio to urinary creatinine concentration. The first urine samples of the morning were preferred to timed overnight collections because in children urinary albumin:creatinine ratios in these morning samples do not change with age.⁶ In contrast, albumin excretion rates increase with age and correlate with height, weight, and surface area.⁷ In this paper we use the term urinary excretion of a protein to indicate the ratio of concentration of that protein to creatinine in the first urine sample of the morning.

The concentrations of α -1-microglobulin were measured by radial immunodiffusion⁸ using an antiserum and standards supplied by Behringwerke Ag (Marburg, Lahn, West Germany). The concentrations of κ light chains were measured by radial immunodiffusion using an antiserum against pooled free κ light chains and standards supplied by the Department of Immunology, University of Birmingham. The standards used are prepared from pooled κ Bence Jones protein and the results are expressed as milliunits (mU) where one mU is equivalent to one milligram of standard. Milliunits are used because free light chains vary in their degree of polymerisation and antigenicity. Radioimmunoassays were used to measure concentrations of albumin (Pharmacia, Albumin RIA 100) and β -2-microglobulin (Pharmacia, β_2 m RIA 100); β -2-microglobulin is degraded at pH <6.0 and was therefore only measured in urine samples of pH $\geq$ 6.0. The limit of sensitivity of the assays were respectively: α -1-microglobulin, 1 mg/l; κ light chains, 10 mU/l; albumin, 0.8 mg/l; and β -2-microglobulin, 0.2 mg/l. Interassay coefficients of variation were respectively: α -1-microglobulin, 6.8%; κ light chains, 13%; albumin, 8.9%; and β -2-microglobulin, 11%. Creatinine was measured by the Jaffe reaction and glucose by an autoanalyser using a glucose oxidase method. Venous blood samples collected within 24 hours of collection of urine samples were assayed for glycosylated haemoglobin by isoelectric focusing.⁹ Statistical analysis was performed using the Mann-Whitney U test and Spearman Rank Correlation test and a two tailed value was taken for estimates of *p*. Values are expressed as median (range).

Results

Urinary excretion of α -1-microglobulin and κ light

chains was significantly higher in children with IDDM compared with normal children (figs 1 and 2). Median urinary α -1-microglobulin:creatinine ratio was 0.57 (0.11–1.92) mg/mmol in children with IDDM and 0.23 (0.11–0.90) mg/mmol in normal children ($p < 0.0002$). Median urinary κ light chain:creatinine ratio was 2.4 (0.4–7.4) mU/mmol in children with IDDM and 1.3 (0.6–4.8) mU/mmol in normal children ($p < 0.0002$). In contrast there was no significant difference in urinary albumin excretion (fig 3); urinary albumin:creatinine ratios were 0.89 (0.06–6.85) mg/mmol for children with IDDM and 0.82 (0.11–3.67) mg/mmol for normal children. Twenty six urine samples from diabetic children and

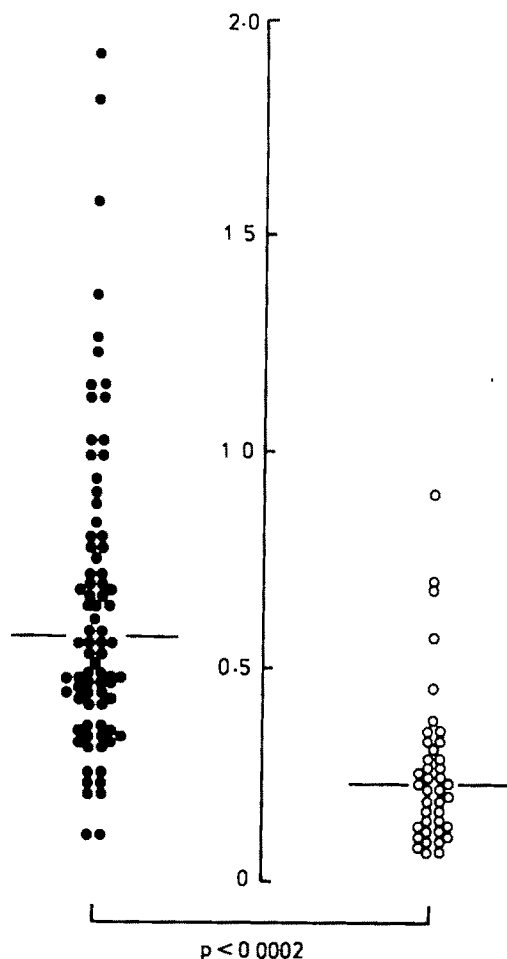


Fig 1 Urinary α -1-microglobulin excretion (mg/mmol creatinine) in 80 children with insulin-dependent diabetes (closed circles) and 40 normal children (open circles). Bars indicate median values.

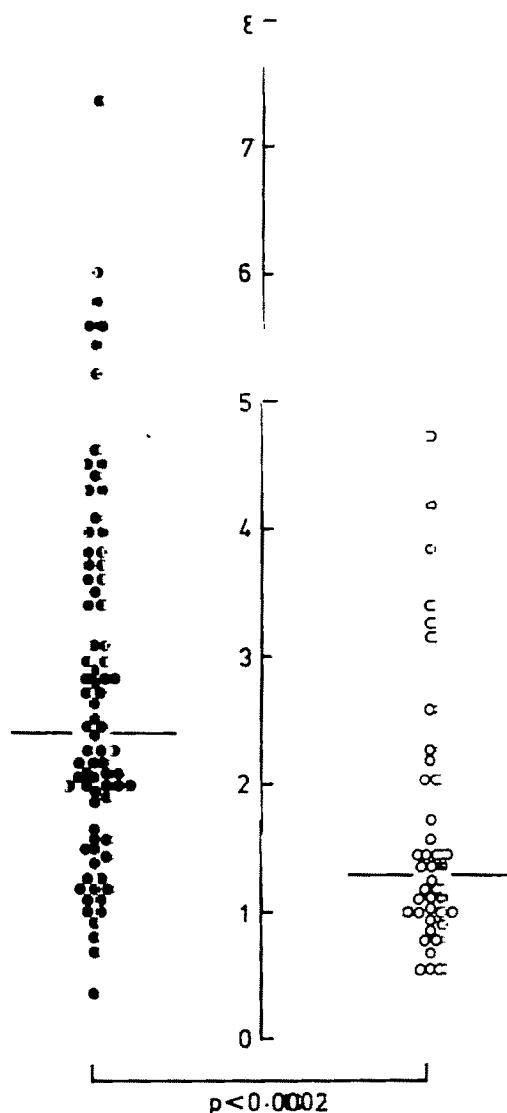


Fig 2 Urinary α light chain excretion (mUmmol creatinine) in 80 children with insulin-dependent diabetes (closed circles, and 40 normal children (open circles). Bars indicate median values

11 urine samples from normal children were of pH ≥ 6.0 . Detectable concentrations of β_2 -microglobulin were present only in five of 26 urines from the diabetic and in one of 11 urines from normal children.

There was a highly significant correlation between urinary excretion of α -1-microglobulin and urinary excretion of α light chains in both children with IDDM ($r_s=0.68$, $p<0.0002$) and normal children

($r_s=0.78$, $p<0.0002$). Urinary albumin excretion did not correlate significantly with urinary excretion of α -1-microglobulin or α light chains either in normal or diabetic children.

In children with IDDM the glycosylated haemoglobin correlated with urinary excretion of α -1-microglobulin ($r_s=0.34$, $p<0.0005$, fig 4), α light chains ($r_s=0.27$, $p<0.05$, fig 5), and albumin

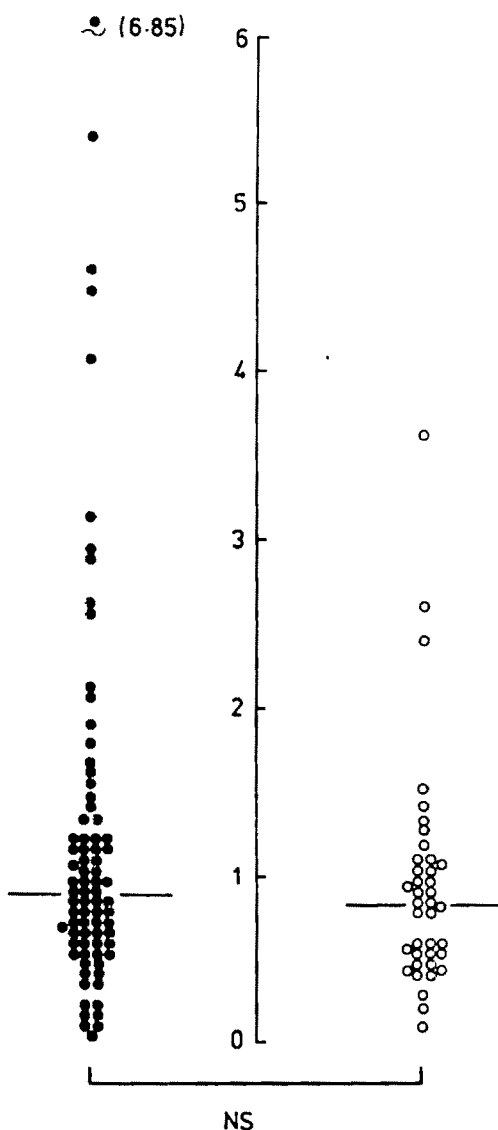


Fig 3 Urinary albumin excretion (mg/mmol creatinine) in 89 children with insulin-dependent diabetes (closed circles) and 40 normal children (open circles). Bars indicate median values

($r_s=0.27$, $p<0.05$). Urinary glucose concentration in children with IDDM correlated with urinary excretion of α -1-microglobulin ($r_s=0.52$, $p<0.0002$, fig 6), and κ light chains ($r_s=0.51$, $p<0.0002$, fig 7), but not with urinary albumin excretion.

Neither age nor duration of diabetes correlated with urinary excretion of α -1-microglobulin, κ light chains, or albumin in children with IDDM. In normal children there was a trend towards a negative correlation of age with urinary excretion of κ light chains ($r_s=-0.34$, $p=0.06$) and age with urinary excretion of α -1-microglobulin ($r_s=-0.31$, $p=0.10$). There were no significant differences between boys and girls in urinary excretion of albumin, α -1-microglobulin, or κ light chains either in children with IDDM or in normal children (table).

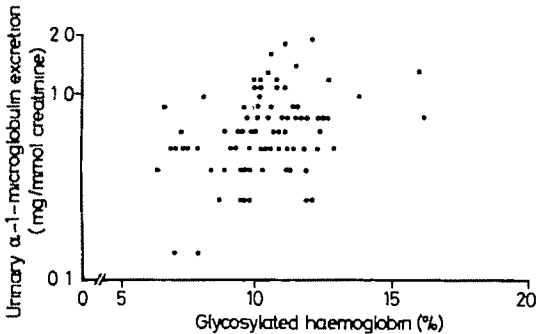


Fig 4 Scatter diagram of urinary α -1-microglobulin excretion (logarithmically transformed to compensate for positively skewed distribution) and glycosylated haemoglobin in diabetic children.

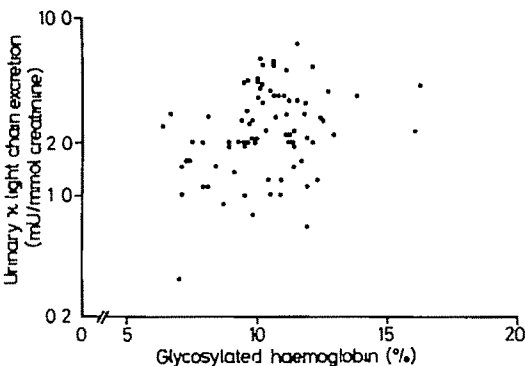


Fig 5 Scatter diagram of urinary κ light chain excretion (logarithmically transformed to compensate for positively skewed distribution) and glycosylated haemoglobin in diabetic children.

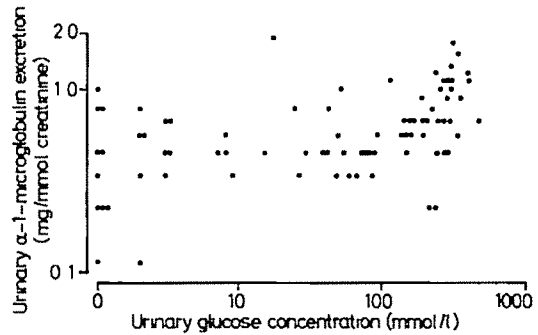


Fig 6 Scatter diagram of logarithmically transformed data for urinary α -1-microglobulin excretion and urinary glucose concentration in diabetic children.

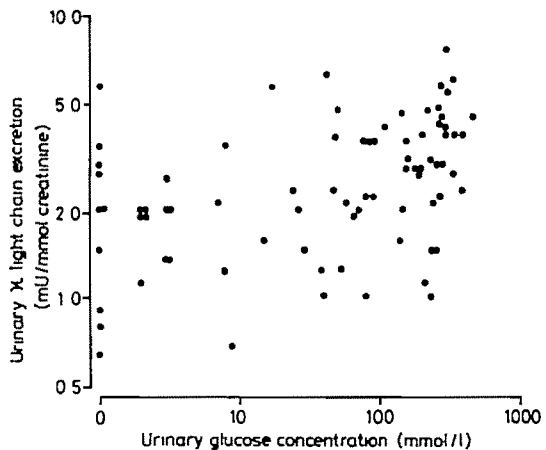


Fig 7 Scatter diagram of logarithmically transformed data for urinary κ light chain excretion and urinary glucose concentration in diabetic children.

Discussion

Children with IDDM have a significantly raised urinary excretion of α -1-microglobulin and κ light chains without a significant rise in albumin excretion, which indicates impaired tubular reabsorption of low molecular weight proteins. There was a strong correlation between urinary excretion of α -1-microglobulin and κ light chains in both the normal and diabetic children but neither correlated with urinary albumin excretion. This is consistent with the expected renal handling of α -1-microglobulin and κ light chains as proteins that are freely filtered by the glomerulus and greater than 95% reabsorbed and catabolised by the proximal tubule.

Previous studies of proximal renal tubular function in diabetes have used urinary excretion of β -2-

Table Urinary excretion of albumin, α -1-microglobulin, and κ light chains in children with insulin-dependent diabetes and in normal children

	Diabetic children			Normal children		
	Boys (n=40)	Girls (n=40)	Boys v girls	Boys (n=19)	Girls (n=21)	Boys v girls
Albumin (mg/nmol creatinine)						
Median	0.81	0.97	NS	0.57	1.00	NS
Range	0.12-6.85	0.06-5.39		0.11-1.40	0.21-3.67	
α -1-microglobulin (mg/nmol creatinine)						
Median	0.60*	0.55*	NS	0.26	0.23	NS
Range	0.23-1.70	0.11-1.92		0.14-0.90	0.11-0.68	
κ light chains (mU/nmol creatinine)						
Median	2.26	2.43*	NS	1.47	1.24	NS
Range	0.68-7.35	0.36-5.54		0.57-4.75	0.57-3.39	

* $p < 0.0002$ compared with normal children of same sex.NS=Not significant, two tailed $p > 0.05$.

microglobulin as an index of proximal tubular function. Normal urinary excretion of β -2-microglobulin in adult diabetics has been reported in several studies.¹⁰⁻¹² Parving *et al.*,¹³ however, found raised urinary excretion of β -2-microglobulin when metabolic control of diabetes was poor and Christiansen *et al.* showed a fall in its excretion during control of glycaemia by an intravenous insulin infusion.¹⁴ Ellis *et al.* reported a raised excretion of β -2-microglobulin in 67 children with IDDM.¹⁵ Miltenyi *et al.* found a raised urinary excretion of β -2-microglobulin in 11 children with diabetic ketoacidosis, but after 10 days its excretion was no longer significantly raised compared with either 13 children with well controlled diabetes or 18 non-diabetic children.¹⁵ Part of the discrepancy between the results of these studies might be due to the properties of β -2-microglobulin. Degradation occurs *in vitro* at pH <6.0. We confined our radioimmunoassay estimation of β -2-microglobulin, however, to urines of pH ≥ 5.5 but found measurable quantities of β -2-microglobulin in only five of 26 diabetic samples. This is in keeping with Teppo and Groop who found that adult insulin-dependent diabetics with normal urinary albumin excretion have increased excretion of κ light chains despite normal excretion of β -2-microglobulin.⁵ Therefore β -2-microglobulin might be an insensitive indicator of proximal tubular reabsorptive function in diabetes.

There are few low molecular weight proteins other than β -2-microglobulin whose excretion has been studied as an index of tubular function in diabetes. The excretion of enzymes, however, which are present in the renal tubular cells but are not in

the glomerular filtrate has been investigated. Excretion of N-acetyl- β -D-glucosaminidase (NAG) a lysosomal enzyme, is increased in IDDM.¹⁷ In children with IDDM urinary leucine aminopeptidase (a brush border enzyme) and urinary NAG activities were higher in diabetic children, even when well controlled, than in non-diabetic children.¹⁶

The possibility of a relation between poor glycaemic control and impaired tubular reabsorption is raised by the weak but significant correlation of glycosylated haemoglobin and the stronger correlation of urinary glucose, with both urinary excretion of α -1-microglobulin and κ light chains. Such a relation would be consistent with experimental evidence. In the rat kidney increases in urinary flow rate reduce tubular protein reabsorption.¹⁸ In man a similar effect might result from the osmotic diuresis associated with hyperglycaemia. In children with IDDM glycosuria is associated with alterations in the tubular transport of sodium, calcium, and phosphate¹⁹ and might directly alter the transport of other substances. It is clearly possible, however, that the relation between urinary glucose and tubular protein reabsorption is one of effect rather than cause, a defect in tubular reabsorption accounting for part of the glycosuria as well as the loss of low molecular weight proteins in urine.

Pathological changes in the proximal convoluted tubule consisting of glycogen-containing vacuoles (Armstrong-Ebstein change) have long been known to occur in diabetes.²⁰ Impaired tubular reabsorption of low molecular weight proteins in children with IDDM, but without evidence of microalbuminuria, indicates that proximal renal tubular function may

be one of the earliest detectable abnormalities of renal function in IDDM. Its relation to other early functional changes in the diabetic kidney, such as increased glomerular filtration, is unknown, and it will require prospective longitudinal studies for proper evaluation.

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Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia

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SUMMARY High doses of intravenous desferrioxamine infused over a short period of time induce a large faecal and urinary iron excretion but also produce retinal abnormalities that are characterised by decreased amplitude on electroretinography and defective dark adaptation. This regimen also results in high faecal iron, zinc, and copper excretion, and reduced granulocyte zinc concentrations and alkaline phosphatase activity. The retinal abnormalities may be related to the zinc and copper deficiency and/or iron depletion 'per se' which interferes negatively with critical iron dependent enzymes.

Subcutaneous infusion of desferrioxamine is the most efficient method for reducing the iron burden in patients with thalassaemia major who are transfusion dependent.¹⁻⁶ The daily infusion of 40-60 mg/kg over 12 hours for six days a week is usually sufficient to obtain iron balance.¹⁻⁴ Because some patients fail to comply with this regimen the additional administration of large doses by intravenous infusion has been proposed.³ High doses of desferrioxamine, either by intravenous or subcutaneous administration, however, may result in optic neuropathy or high frequency sensorineural hearing loss, or both.^{7,8} Likewise, in rabbits anaesthetised with urethane, the intravenous infusion of large doses of desferrioxamine produced a reversible reduction in the amplitude of the electroretinogram.⁹ Toxic concentrations are probably reached when the dose of desferrioxamine administered is disproportionately high in relation to the amount of iron available for chelation. In these conditions desferrioxamine may chelate critical trace elements such as copper and zinc,¹⁰ the depletion of these elements may be responsible for the neurotoxic effect of the drug.

In this study we monitored the development of ocular abnormalities and possible zinc or copper depletion, or both, in a group of patients with thalassaemia major who were chelated with desferrioxamine by a combination of traditional daily subcutaneous infusion and monthly intravenous administration of large doses because of failure to

comply with the regimen of subcutaneous administration.

Patients and methods

Fifteen children, aged from 9 to 16 years, with transfusion dependent thalassaemia major and moderate iron overload (serum ferritin concentrations from 1100 to 2000 µg/l), because of low compliance with daily infusion of subcutaneous desferrioxamine, were treated by a combination of traditional daily subcutaneous infusion and monthly intravenous administration of very large doses according to a previously published scheme.¹¹ Each patient was treated for 10 consecutive months but the balance study (see later) was carried out only once.

The dose of desferrioxamine for subcutaneous infusion was 40-60 mg/kg over a period of 12 hours each night for six days a week. The intravenous infusion was given over a period of 24 hours at the dosage of 10-12 g (200-450 mg/kg) dissolved in 750 ml of 5% glucose solution. Urinary and faecal iron concentrations, zinc and copper excretion, serum zinc pattern, leukocyte zinc concentrations, and alkaline phosphatase activities were analysed only once, as detailed later, before and after the infusion of intravenous desferrioxamine when we introduced the combination of both intravenous and subcutaneous administration

Ophthalmic evaluation was also carried out before and after the termination of the infusion, but this assessment was repeated from two to three times at times of successive intravenous infusion and again one, two, and three months after we interrupted the intravenous infusions while continuing the subcutaneous administration.

OPHTHALMOLOGIC ASSESSMENT

The ophthalmic assessment included determination of the best corrected visual acuity by standard methods, pupillary reaction, ocular motility, slit lamp examination for changes in the anterior segment, and visual field measurement on a calibrated Goldman kinetic perimeter with light intensity regulated at 31.5 apostilb. A decrease above 20% in the average peripheral extent of the field in at least two quadrants was considered abnormal. Adapted electroretinograms were obtained according to Babel¹² with flashes of white light of constant colour range and intensity of 2 joule, 1 hertz/second at 30 cm from ocular plane (Pantops 200-Ferlux Instruments). The amplitudes of the response were considered abnormal when the value was decreased more than 20% from normal values (190 (SD15) μ V). During dark adaptation, after a preliminary light adaptation, we noted the stage at which the amplitude of the slow scotopic positive wave (the scotopic components of the electroretinogram are mainly due to the activity of the rods in dark adaptation) reached that of the photopic component. This is referred to as the 'transition phenomenon,' which is a valuable sign for the judgment of the scotopic function.¹³

METABOLIC STUDIES

In order to carry out copper, zinc, and iron balance studies each patient was admitted to the hospital for a week. With the aim of eliminating any residual effect of the subcutaneous infusion the day before admission the daily infusion of subcutaneous desferrioxamine was interrupted. While in the hospital the patients were on a strict controlled diet containing roughly 8–10 mg/day iron, 0.1 mg copper/kg body weight, and 0.3–0.4 mg zinc/kg body weight. Diet and collection of the urine and stool were carefully controlled by nurses who were specifically instructed to avoid any faecal contamination with urine. Collection periods of stools were defined by administering radio-opaque markers.

Precautions against environmental contamination were taken for all diet, blood, urine, and stool collections and analyses. Specimens were stored only in plastic containers and only low mineral content water and ultra high purity reagents were used in sample and standards preparation; before

use, all glassware and plastic containers were acid washed in 1.0 N hydrochloric acid for 30 minutes and rinsed six times in deionised water.

Blood samples from peripheral veins were collected with plastic syringes and stainless steel needles and put into plastic tubes. Serum and granulocyte zinc concentrations and granulocyte alkaline phosphatase activity were measured in samples taken before and at the end of the intravenous infusion as well as one month later.

Basal iron, zinc, and copper excretion were evaluated in urine and faeces collected for three days before the infusion of desferrioxamine. The effect of this infusion was determined by measuring these elements in the urine and faeces collected on the day of the infusion as well as three days after. During this study period the subcutaneous infusion was interrupted.

An aliquot of the preinfusion and postinfusion urinary pools was prepared and frozen for further analysis. The faeces were homogenised with a known amount of deionised water. An aliquot was removed and dried at 100°C overnight and then ashed in a muffle furnace at 550°C and left overnight. The resultant ash was dissolved with 10% hydrochloric acid, transferred to a volumetric flask, and made up to volume with demineralised water.

Serum, urinary, and faecal iron, zinc, and copper were determined by atomic absorption (IL 551 Spectrophotometer). Granulocyte alkaline phosphatase activity was assayed with p-nitrophenyl-phosphate as substrate according to It-Koon and Moss.¹⁴ Granulocytes were separated from the other blood cells according to Boyum.¹⁵ The specimens used for the analysis contained a percentage of granulocytes varying from 90 to 100%. Statistical analysis was carried out by Student's paired *t* test.

Results

OPHTHALMOLOGIC EVALUATION

Visual acuity and average field size were normal in all subjects. No isolated field defect (scotomata) or enlargement of the blind spot were detected. Fundoscopy showed no pigment abnormalities, focal lesions, macular oedema, or unusual vascular patterns. In three patients the electroretinograms showed a decreased amplitude before and at the end of the desferrioxamine infusions as well as at follow up examinations carried out at one, two, and three months later. Seven patients, who had a normal electroretinogram before the infusion, showed a decreased amplitude at the evaluation carried out when the infusion was terminated. The same pattern was recorded at least twice at each successive infusion. In these subjects a normal

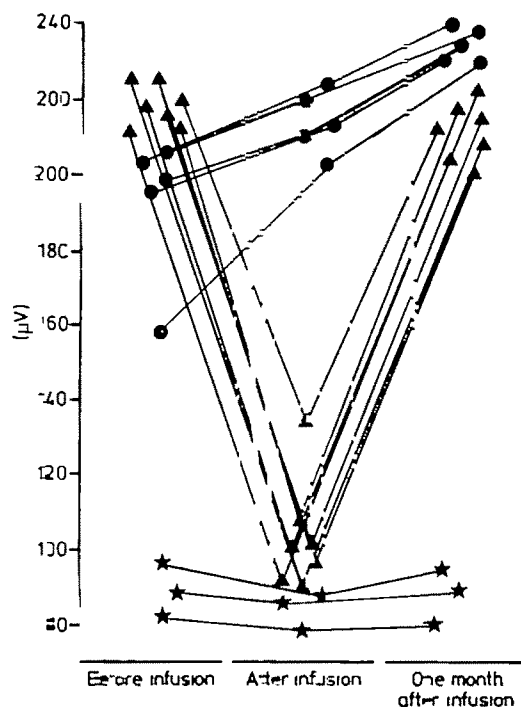


Fig. 1 Effect of intravenous infusion of desferrioxamine on the amplitude on electroretinography. Patients with normal amplitude (●), patients with transiently decreased amplitude (▲), and patients with persistent decreased amplitude (★).

electroretinogram was seen at follow up examination after the termination of intravenous treatment (fig. 1).

In the three patients with permanent abnormalities shown on their electroretinograms and in six out of the seven with the transient effects we noted when control measurements were taken immediately after infusion of intravenous desferrioxamine a 'transition phenomenon' appeared after 14 to 18 minutes in the dark. In our age matched controls this phenomenon occurred from a minimum of 8 to a maximum of 10 minutes. The remaining five patients did not show any abnormalities of their electroretinograms.

METABOLIC STUDIES

Fig. 2 shows the effect of the intravenous infusion of desferrioxamine on serum zinc concentrations. The patients were divided into three groups: those with no retinal abnormalities, those who showed a decreased amplitude on an electroretinogram after infusion of desferrioxamine, and those with permanent abnormalities shown on an electroretinogram. During the 24 hours of the infusion all serum zinc concentrations fell to within the normal ranges (84% (SD 12) $\mu\text{g}\%$ (12.9 (1.8) $\mu\text{mol/l}$)). During this period fluctuations in zinc concentrations occurred with peak concentrations in the morning and the lowest concentrations in the afternoon. No significant differences in the zinc concentrations or the

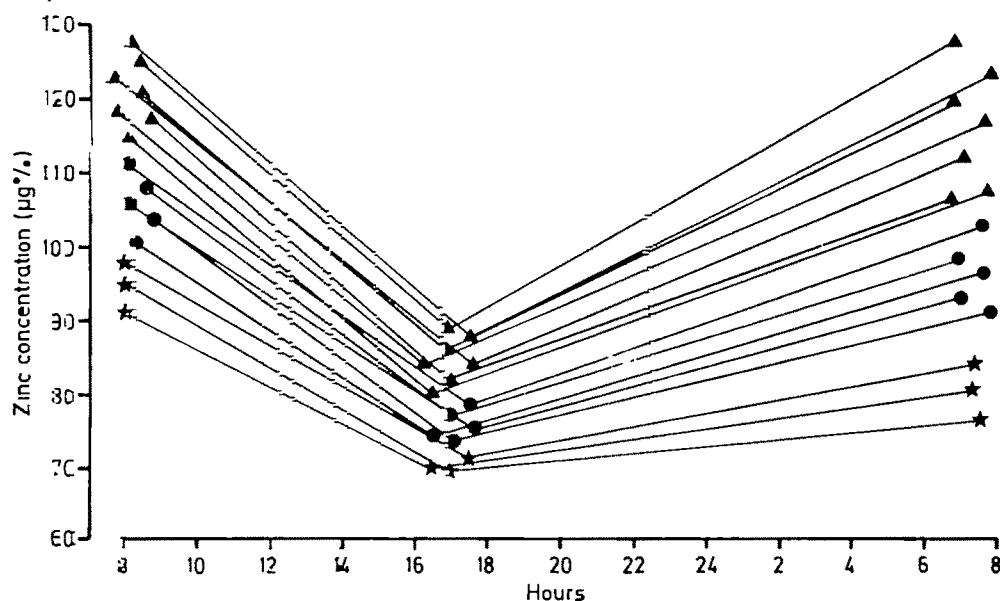


Fig. 2 Effect of intravenous infusion of desferrioxamine on serum zinc concentrations. Patients with normal amplitude on electroretinography (●); patients with transiently decreased amplitude (▲); and patients with persistent decreased amplitude (★). Results are in $\mu\text{g}\%$, to convert to $\mu\text{mol/l}$ multiply by 0.153.

zinc pattern were observed between the three groups of subjects investigated

The effects of desferrioxamine infusion on iron, zinc, and copper excretion are summarised in fig 3. After infusion of desferrioxamine there was a significant ($p<0.001$) increase of mean urinary and faecal iron excretion. On average 45% of the iron was eliminated through the urine and 55% with the stools. After the infusion, faecal and urinary zinc and copper excretion were also significantly increased ($p<0.001$ and <0.05 , respectively). Considering all the patients together no significant correlation was observed between zinc and iron elimination both in faeces and urine.

If the patients were divided according to the abnormalities shown on their electroretinograms—that is, the first group without abnormalities, the second group with transitory alterations after intravenous infusion, and the third group with permanent abnormalities—it can be seen that the second group of patients had significantly ($p<0.05$) higher mean urinary zinc elimination compared with the first group; there were no differences observed in iron and copper elimination. Mean faecal excretions of all the three trace elements were significantly higher in the second group ($p<0.001$ for iron

and zinc; $p<0.01$ for copper) than in the first group ($p<0.01$). In the second group there was an inverse correlation between total zinc and iron elimination; this, however, did not reach significance. Those subjects who had persistent abnormalities on their electroretinograms had less iron, copper, and zinc excretion both in urine and faeces when compared with the other two groups.

In all patients granulocyte zinc content and

Table Effect of intravenous infusion of desferrioxamine on zinc concentrations and alkaline phosphatase activity in granulocytes

	Zinc ($\mu\text{mol/g}$ protein)	Alkaline phosphatase activity ($\mu\text{M/minute/g}$ protein)
	<i>Patients with thalassaemia</i>	
Basal*	6.53 (1.83)	20 (8.21)
At the end of the infusion†	-4.86 (1.8)	-15.23 (9.15)
1 month after infusion*	0.41 (2.27)	2.36 (14.5)
	<i>Controls</i>	
	6.92 (1.75)	23 (3.8)

*Results are mean (SEM)

†Results are mean differences from the basal value (standard errors of the differences)

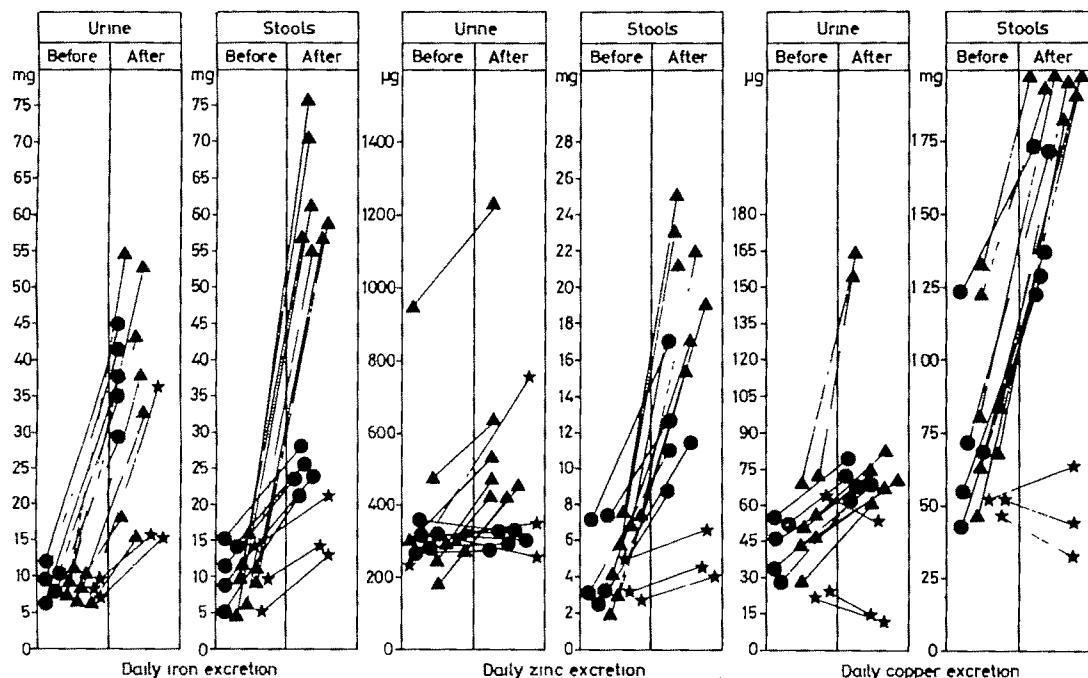


Fig 3 Effect of intravenous infusion of desferrioxamine on iron, copper, and zinc excretion. Patients without abnormalities on electroretinography (●); patients with transitory alterations (▲); patients with permanent abnormalities (★). Patients had baseline concentrations higher than normal because they had stopped subcutaneous administration of desferrioxamine only 24 hours previously

alkaline phosphatase activity were within the normal ranges at the outset of the infusion and decreased significantly ($p < 0.001$) at the end, and they returned to normal values at the determination carried out one month later (table 1). No significant differences were noted between the three groups.

Discussion

This study shows that high doses of intravenous desferrioxamine infused over a short period produce a reversible minor toxic effect on the retina, which is characterised by reduced amplitude on adapted electroretinography and defective dark adaptation. More severe retinal or optic nerve toxicity, or both, that consisted of night blindness, field defects, visual loss, loss of colour vision, and delayed visual evoked potential has been detected after intravenous or subcutaneous infusion of similar large doses of desferrioxamine for a prolonged period.^{7,8} Follow up studies in some of these patients showed evidence of evolution towards the pigmentary degeneration of the retina indicating toxicity at the level of retinal pigment epithelium.¹⁶

The fluctuations in the serum zinc concentration that are seen during infusion of desferrioxamine are probably not related to administration of the drug as they are very similar to the daily variations in serum zinc concentrations found in normal subjects (circadian rhythm).¹⁷

In this investigation large doses of intravenous desferrioxamine produced a consistent increase in iron excretion as has been found in previous studies^{3,11} but resulted also in increased elimination of zinc and copper. Intravenous desferrioxamine had more effect on the faecal loss of iron, zinc, and copper than it had on their urinary loss. We can exclude the possibility that this pattern may be due to urine contamination of faeces during collection because during the balance study the patients were in the hospital and urine and faecal collections were carefully controlled by a nurse who had been adequately instructed. Furthermore it is already known from a study carried out by Pippard *et al* that large doses of desferrioxamine result in an increase of faecal iron loss but have little effect on urinary elimination.¹⁸ An inverse but not significant correlation between iron and zinc excretion was observed solely in those subjects with transient abnormalities on electroretinography.

Increased copper and zinc excretion may be explained by assuming that the rapid infusion of large doses of desferrioxamine left a certain amount of the drug non-iron chelated and thus able to chelate these trace elements. Accordingly granulocyte alkaline phosphatase activity, which is one of the best indicators of the zinc content of the

organism¹⁹ decreased significantly after the infusion of desferrioxamine. We cannot exclude, however, that at least partially, the decrease of leukocyte alkaline phosphatase activity may be caused by a possible interference of residual desferrioxamine in the assay of this zinc dependent enzyme.

The depletion of iron, zinc, and copper may be related to the retinal abnormalities. Experimental and clinical evidence indicate the importance of zinc in the maintenance of normal visual function.^{19,20} First of all the highest concentration of zinc and several zinc-containing enzymes are present in the retinal epithelium.^{19,20} Zinc deficiency in rats produces accumulation of osmophilic inclusion bodies containing vitamin A derivatives and degeneration of the photoreceptors outer segments.²¹ Optic atrophy has been described in acquired zinc deficiency due to malabsorption as well as in acrodermatitis enteropathica.²² Defective dark adaptation responsive to zinc treatment has been reported in sickle cell anaemia patients in whom leukocyte zinc concentration was low.¹⁹⁻²³ Several drugs, notably di-iodohydroxyquinoline and penicillamine, which produce toxic optic neuropathies are also potent metal chelators.²² Abnormalities of zinc metabolism have been described also in retinitis pigmentosa.²⁴ There are several mechanisms whereby zinc deficiency may produce deleterious effects on the retinal pigment epithelium. Zinc by decreasing alcohol dehydrogenase enzyme activity may in turn produce an increased uptake of vitamin A.²¹ The resulting accumulation of retinal and its esters may cause release of lysosomal enzymes.²¹ Zinc deficiency also enhances lipid peroxidation and impairs the metabolism of amino acids, nucleic acids, and proteins.¹⁹⁻²¹ Although our data have not established a clear relation between zinc deficiency and ocular abnormalities, they suggest, however, that zinc depletion induced by desferrioxamine in the retinal pigment epithelium may have played a part in producing the transient abnormalities that we have seen on electroretinography.

Blake *et al*, who studied a patient with retinal toxicity induced by desferrioxamine, also found abnormalities in the loosely bound iron and copper content of the cerebrospinal fluid.²⁵ Copper and iron complexes may stimulate an autocatalytic process of lipid peroxidation and might therefore be responsible for retinal abnormalities in patients treated with desferrioxamine.²⁶

Desferrioxamine acts on a labile iron pool, which is presumably intermediate in the interchange of iron molecules between storage and transport forms.²⁷ Acute iron depletion of this pool may have a negative effect on the iron dependent enzymes and

help cause the production of retinal anomalies. We have excluded the possibility that ocular abnormalities in our patients were related to a diabetic or prediabetic condition via the disruption of the integrity of the blood-retinal barrier, as has been proposed,²⁸ because none of our patients had a reduced glucose tolerance (data not shown).

A limited number (three out of 15) of the patients investigated showed persistent abnormalities on electroretinography. Because it is difficult to assess the compliance to treatment we do not know whether these patients differed from those with transient abnormalities in the amount of desferrioxamine they received by the daily subcutaneous infusion in the years preceding the trial. Those patients with persistent abnormalities did not differ, however, from those with transient modifications in the serum ferritin concentrations, the zinc content, and alkaline phosphatase activity of leukocytes, but showed lower zinc and iron excretion after intravenous infusion of desferrioxamine. This may indicate the presence of less iron accumulation and a borderline zinc reserve, which may nevertheless result in defective function of those tissues, such as the retinal epithelium, which are most sensitive to zinc depletion.

In conclusion, administration of large doses of desferrioxamine by intravenous infusion are able to produce in iron overloaded thalassaemia patients a very large iron excretion but they also induce excretion of trace elements such as copper and zinc and cause transient ocular abnormalities. For those patients treated with this regimen ophthalmological evaluation is recommended for determining early retinal toxicity induced by desferrioxamine. Further studies are needed in order to assess whether a reduction of the desferrioxamine dosage may avoid these toxic effects.

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Arm fat and muscle areas in infancy

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SUMMARY Growth of arm muscle, fat and water areas were evaluated longitudinally in a prospective study in 81 infants from birth to the age of 12 months. The percentage of arm fat area on the cross sectional upper arm area increased at the age of 15 days with a peak at the age of 6 months while arm muscle area increased progressively throughout the year. As arm water area represented only 1% of cross sectional upper arm area, calculations of arm fat and muscle areas can be carried out from measurements of mid arm circumference and tricipital skinfold at 15 seconds. Percentiles are presented for the upper arm fat and muscle areas, which can be used as index for the infants' nutritional state.

The evaluation of the nutritional state of infants is an important problem because according to Merritt and Susskind one third of infants in hospital are at risk from malnutrition.¹ Recently anthropometric evaluations of the upper limb have become useful as indicators of the nutritional state of children and adults. It is assumed that the triceps skinfold thickness indicates the calorie reserve and the arm size reflects the reserve of protein.²⁻⁴ Gurney and Jelliffe pointed out that the cross sectional arm areas represent better estimates of the relative contribution of fat and muscle to the total arm area than mid arm circumference and triceps skinfold.⁴ To our knowledge there is no report of these arm areas measured at birth and then measured regularly throughout the first year of life. Therefore the first aim of this study was to report these mid arm fat and muscle areas from measurements collected prospectively in a population of 100 infants and to provide preliminary norms for the nutritional state of infants.

In neonates Thornton *et al* showed that the dynamic change of tricipital skinfold thickness is related to extracellular water content.⁵ It is not known to what extent these dynamic changes could influence the results of arm fat and muscle areas during infancy. The second aim of this study was therefore to look at this dynamic change in tricipital skinfold thickness in order to evaluate its magnitude.

Subjects and methods

This prospective longitudinal study was designated for a target number of 100 infants born at the Centre

Hôpitalier Lucien Hussenot of Vienne (Isère, France) between 2 January 1984 and 30 December 1985. The following conditions were required for inclusion into the study: parent's informed acceptance and good comprehension of the French language and parents living within 20 km of the town. The neonates who were included were born at full term with a birth weight of more than 2500 g, an Apgar score >6 at 5 minutes, and with no detectable malformation at clinical examination. Measurements were taken at birth (that is, before 3 days of age), and follow up measurements at 15 days ($\pm$ three days); one month ($\pm$ three days); and at four, six, nine, and 12 months ($\pm$ seven days). Unscheduled losses, however, occurred during the study mostly because of a refusal to continue the study, or the family changed address, and the practical impossibility of keeping to the scheduled timing. Altogether 81 neonates were finally included in the study and 64 infants were measured at the age of 12 months. This sample had a large representation of families of high socio-economic state as 88% of the fathers belonged to the second or third category of the classification of Goujard *et al*⁶—that is, civil servants, trained personnel, tradesmen, and farm owners. An analysis of dietary data showed that the proportion of breast fed infants was 75% at birth, 59% at the age of 15 days, 45% at the age of one month, 30% at the age of 2 months, and 7% at the age of 4 and 6 months. The formula milks given were in agreement with the recommendations of the European Society for Pediatric Gastroenterology and Nutrition (ESGAN) but at the age of 6 months 33% of the infants were given their diet as half cream cows' milk; this increased 42% at the age of 12 months.

Additional intake was not evaluated in each case with adequate precision.

All measurements were collected in hospital or at home by one of us (MD). All upper arm measurements were done on the left side at exactly the mid distance between the acromion and the tip of olecranon. Weight was measured with a SECA-745 A balance to the nearest 10 g. Length of body was determined with a SECA-somatometer to the nearest 0.5 cm. Head and mid arm circumferences were evaluated to the nearest mm using a plastic tape. All these measurements were done according to the methods of Sempé *et al.*⁷ Tricipital and scapular skinfold were measured with a Harpenden caliper using the technique of Brans *et al.*⁸ Measurements to the nearest 0.1 mm were obtained exactly 15 and 60 seconds after application of the caliper. The coefficient of variation of each measurement was lower than 5% with ranges between 1.5% for the mid arm circumference to 4.5% for the tricipital skinfold.

The calculated items included arm areas according to the equations given by Gurney and Jelliffe.⁴ They assume that the upper arm is cylindrical in form and that no variation occurs in humeral diameter. Slight modifications of the equations were introduced to allow consideration of the dynamic changes of tricipital skinfold: the timing of the measurement is not normally considered in the equations but in the present study arm muscle area (AMA) was determined from the tricipital skinfold measured at 15 seconds (TSKF15), and the arm fat area (AFA) was calculated from the tricipital skinfold measured at 60 seconds (TSKF60). The

findings of Brans *et al.*⁸ and Thornton *et al.*⁵ on the dynamic changes of tricipital skinfold showed that in neonates skinfold thickness compressibility or expressibility is intimately related to extracellular water content of the body. Therefore we estimated the arm water area (AWA) from the total area with the subtraction of AMA (measured from TSKF15) and of AFA (measured from TSKF60).

Thus: Arm area:

$$AA = MAC^2 / 4\pi$$

Arm muscle area:

$$AMA = (MAC - \pi \text{ TSKF15})^2 / 4\pi$$

Arm fat area:

$$AFA = AA - \frac{(MAC - \pi \text{ TSKF60})^2}{4\pi}$$

Arm water area:

$$AWA = AA - AMA - AFA$$

The results are all expressed in mm

The results are expressed as mean (SD). Statistical comparisons were carried out using the test of Kruskal and Wallis.

Results

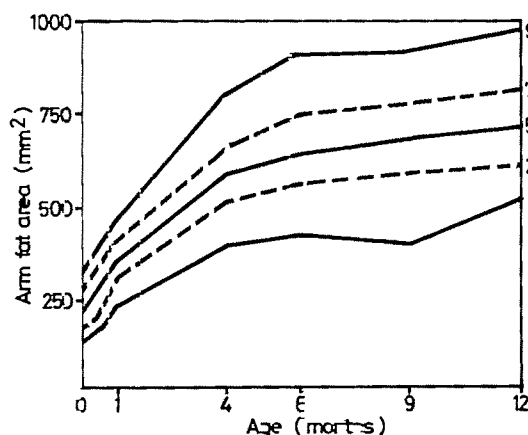
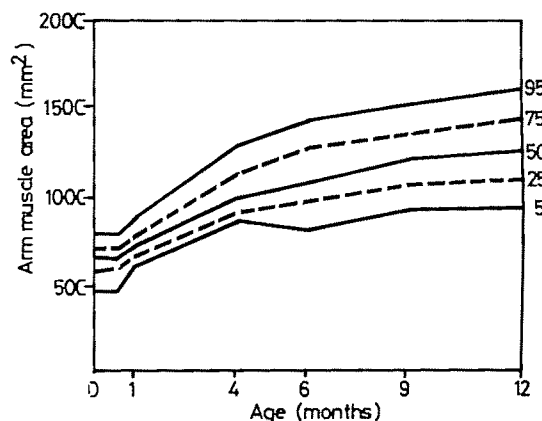
Anthropometric measurements are given in table 1. A significant difference between girls and boys was found for each measurement at each age with the exception of age 15 days and mid arm circumference from birth to 1 month of age. The results of tricipital skinfold at 60 seconds and the different arm areas are shown in table 2. The only significant difference between girls and boys was observed for arm muscle

Table 1 *Anthropometric data of the infants studied (mean (SD))*

Age	Sex (No)	Weight (g)	Length of body (cm)	Head circumference (cm)	Mid arm circumference (cm)
Neonate	Boys (32)	3318 (334)	50.0 (1.3)	34.9 (1.2)	10.4 (0.7)
	Girls (49)	3110 (416)	49.2 (1.6)	34.1 (0.9)	10.2 (0.8)
15 days	Boys (25)	3665 (372)	51.7 (1.5)	36.3 (1.0)	10.7 (0.7)
	Girls (42)	3482 (431)	51.0 (1.8)	35.5 (1.0)	10.6 (0.8)
1 month	Boys (27)	4261 (352)	53.9 (1.3)	37.7 (0.8)	11.6 (0.7)
	Girls (46)	4008 (437)	52.9 (1.8)	36.9 (0.7)	11.3 (0.8)
4 months	Boys (30)	6890 (646)	63.4 (1.7)	42.6 (0.9)	14.3 (0.9)
	Girls (39)	6319 (724)	62.0 (2.4)	41.1 (0.8)	13.8 (1.1)
6 months	Boys (27)	8036 (770)	67.6 (1.8)	43.3 (1.0)	15.0 (1.2)
	Girls (42)	7259 (834)	65.6 (2.4)	42.9 (1.0)	14.2 (1.0)
9 months	Boys (25)	9128 (716)	70.9 (1.9)	45.9 (1.1)	15.6 (1.0)
	Girls (39)	8356 (874)	69.6 (2.4)	44.6 (1.2)	14.8 (1.0)
12 months	Boys (25)	10070 (960)	75.5 (2.2)	47.4 (1.1)	15.7 (1.2)
	Girls (39)	9320 (963)	73.4 (2.5)	45.6 (1.0)	15.3 (0.9)

Table 2 *Results of measurements taken throughout the study (mean (SD))*

Age	Sex (No)	Tripodal skinfold thickness at 60 seconds (mm)	Arm area (mm ²)	Arm muscle area (mm ²)	Arm water area (mm ²)	Arm fat area (mm ²)	Arm fat area (%)
Neonate	Boys (32)	4.20 (1.7)	864 (116)	643 (89)	15.0 (5.7)	205 (42)	23.7 (3.4)
	Girls (49)	4.15 (1.3)	835 (135)	617 (91)	17.7 (7.4)	200 (51)	23.7 (3.3)
15 days	Boys (25)	5.10 (1.3)	916 (129)	645 (91)	16.9 (5.7)	254 (52)	27.6 (3.7)
	Girls (42)	5.30 (1.9)	906 (138)	628 (91)	17.3 (7.5)	261 (55)	28.7 (3.8)
1 month	Boys (27)	5.80 (1.9)	1078 (138)	746 (95)	19.1 (8.8)	313 (61)	28.9 (3.7)
	Girls (46)	6.40 (1.2)	1022 (143)	674 (96)	18.2 (8.2)	331 (72)	32.2 (4.3)
4 months	Boys (30)	8.90 (1.3)	1644 (212)	1047 (161)	19.8 (6.6)	577 (100)	35.1 (4.4)
	Girls (39)	8.60 (1.5)	1522 (242)	962 (177)	25.4 (11.0)	534 (110)	35.1 (5.0)
6 months	Boys (27)	9.50 (1.5)	1804 (280)	1132 (193)	23.7 (11.4)	647 (135)	35.9 (4.5)
	Girls (42)	9.60 (1.1)	1613 (218)	977 (131)	22.8 (10.0)	612 (150)	37.7 (6.1)
9 months	Boys (25)	9.60 (1.4)	1942 (262)	1243 (208)	22.6 (8.8)	676 (111)	34.9 (4.5)
	Girls (39)	9.13 (1.1)	1741 (226)	1113 (163)	18.8 (7.9)	610 (154)	34.8 (6.8)
12 months	Boys (25)	9.23 (1.3)	1986 (318)	1300 (253)	25.0 (10.5)	660 (112)	33.5 (4.0)
	Girls (39)	9.70 (1.1)	1872 (226)	1184 (163)	19.2 (8.0)	669 (157)	35.6 (6.4)

Fig 1 *Evolution of arm fat area during infancy (in percentile)* $AF A = AA - AMA$ $AA = \frac{MAC^2}{4\pi}$ Fig 2 *Evolution of arm muscle area in male infants (in percentile)* $AMA = \frac{(MAC - \pi TSKF)^2}{4\pi}$

area, which was greater in boys from the age of 1 month to 9 months of age. A significant increase of arm fat area was observed in each sex at the age of 15 days with a peak at the age of 6 months.

At birth and subsequently the arm water area represented only a minor part of total arm area since it was only 1% of the arm area. Therefore arm water area could be excluded from the calculations of both arm fat and arm muscle area. The figures give the new equations with TSKF¹⁵ and show the results expressed in percentile.

Discussion

The methodological problems of this investigation are typical of longitudinal studies.⁹ The variability of measurement was avoided as much as possible as all measurements were carried out by the same investigator throughout the study. Additional studies also showed that the population was very homogenous.¹⁰ In addition, the usual anthropometric measurements were very close to the reference curves of French children of Sempé *et al.*⁷ We therefore

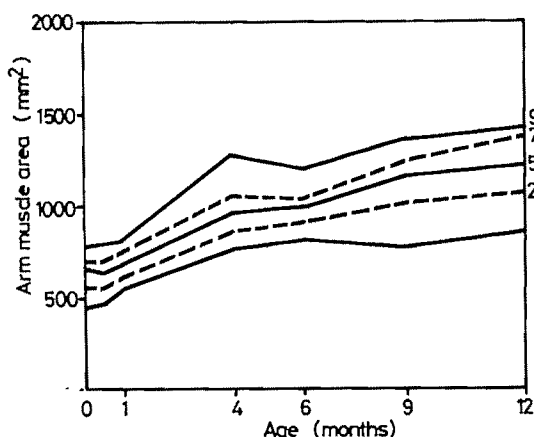


Fig 3 Evolution of arm muscle area in female infants (in percentile). $AMA = \frac{(MAC - \pi TSKF)^2}{4\pi}$

believe that these preliminary results are fairly representative of French infants.

The advantage of arm area over arm circumference and tricipital skinfold deserves some comments. Frisancho showed that these measurements do not estimate the magnitude of the tissue changes in the upper arm.¹¹ This is due to the fact that for a given thickness of subcutaneous fat it takes more fat to cover a large limb than it does to cover a smaller limb. This is particularly important during infancy when there is a fourfold increase in fat body store in the reference male infant during the first six months of life;¹² in male infants we showed a 50% mean increase in mid arm circumference, a 112% mean increase in tricipital skinfold, and the arm fat area increased threefold. Thus these results suggest that the arm fat area gives a more accurate evaluation of the evolution of the body fat accumulation; this finding is in agreement with the result showing that fat areas are systematically better estimators of weight of fat than skinfold thickness in children and adults.¹³

The equations for calculation, however, imply some assumptions such as the cylindrical form of the arm and the constant ratio of arm and humerus diameter. Recently an investigation using computed tomography was applied to adults and led to corrected equations for arm muscle area.¹⁴ The relevance of these corrected equations is unknown in infants, and to evaluate the influence of skinfold thickness compressibility and the role of interstitial water we introduced the dynamic change of tricipital skinfold in relation to total arm area. The present investigation shows that despite the large extracellular water component in young infants¹² changes

in tricipital skinfold and arm water area provide marginal information. As arm water area represented only 1% of total arm area, we consider that it can be neglected in the evaluation of other arm areas and TSKF15 can be used in the calculations. This suggests that in infants the difficult measurement at 60 seconds is not required.

Walker and Hendricks recently stressed the utilisation of arm areas in the evaluation of the nutritional state of infants.¹⁵ To our knowledge there are only two publications concerning infants: the standard based on data collected in the Ten State Nutrition Survey in the United States³ and the report of Martorell *et al* in Guatemala¹⁶; none of these studies were longitudinal and neonates were not measured. In the North American investigation only two determinations were obtained during the first year of life. The Guatemalan children could not provide normal values as some of them were undernourished.

The present results of measurements of arm areas are helpful in the evaluation of the nutritional state of infants. For example, an 8 month old slim looking boy with a weight of 6950 g, a mid arm circumference of 138 mm, and a tricipital skinfold of 6 mm would be at -1.5 SD for weight and mid arm circumference and at the 30th percentile for tricipital skinfold. If his arm fat area was 386 mm², below the 5th percentile and suggesting depletion of calorie reserves, but his arm muscle area was 1129 mm², this would show an adequate protein reserve. In a 4 month old girl with weight at -3 SD (4500 g), and mid arm circumference at -3 SD (107 cm)—tricipital skinfold of 6 mm was not suggestive of depleted fat reserve; however, an arm fat area of 288 mm² was below the 5th percentile and so was the arm muscle area (623 mm²). A third example shows the evaluation of protein reserves: a 9 month old breast fed girl weighed 6500 g (-2 SD), had a tricipital skinfold of 11.4 mm, and an arm fat area of 661 mm², and they were around the 60th percentile; but despite a normal mid arm circumference of 133 mm (-1 SD) the arm muscle area was low at 747 mm² suggesting limited protein reserve. Thus measurements of arm areas are better indicators of fat and protein reserves than tricipital skinfold and mid arm circumference. In addition, measurements of the different arm areas can indicate whether it is the calorie or protein reserve that is involved in insufficient growth. Finally, as low measurements of arm areas are observed before inadequate weight gain they could help in the recognition and detection of marginal reserve depletion.

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Free Running Asthma Screening Test

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SUMMARY The free running asthma screening test (FRAST) was evaluated in 503 Sheffield schoolchildren aged 6 to 12 years and compared with responses to an asthma questionnaire. The FRAST measured peak expiratory flow rate (PEFR) before and at 1, 5, and 10 minutes after maximum voluntary running for at least 5 minutes in a standardised environment. A fall in PEFR of >15% in at least two postexercise readings was defined as abnormal. Six (1%) children did not do the test and 69 (14%) failed to complete it. Of these, 14 were known asthmatics, 18 were not testable, and 37 were normal when retested. There were 14 abnormal FRAST results among 412 'normal' children who completed the test and 10 of these were subsequently diagnosed asthmatic. None of 14 children with an abnormal FRAST result had been identified as wheezy, chesty, or asthmatic in the questionnaire. In this sample there was, on average, one child in every school class with unrecognised exercise induced bronchospasm. The FRAST is an acceptable, feasible, and cost effective way of identifying such potential asthmatics at school.

Screening tests for childhood asthma could improve the management of a condition that is currently underdiagnosed and undertreated.^{1 2} Relatively few 'campaigns against asthma' have been undertaken in children, however,^{3 4} mainly because no simple objective method for assessing wheezing illness in the community has been available.⁵ Screening for asthma by questionnaire may be informative but is inevitably subjective. Provocation tests using bronchoconstrictor drugs or formal exercise protocols are objective, but they are not feasible in a community setting. The free running test is generally considered to be the most bronchoconstrictive of the various exercise challenges and is appropriate for field use.^{6 7} In the present study we have applied the free running test to a large sample of schoolchildren to determine its value as a screening test for wheezing illness in childhood and have compared the results with response to an asthma questionnaire.

Subjects and methods

A standardised exercise test called the Free Running Asthma Screening Test (FRAST) was applied to a sample of schoolchildren aged 6 to 12 years over a six week period during the pollen season (April–May 1985). The children and their parents were informed in advance about the nature, purpose, and date of the test. At the same time written parental consent

was requested and a questionnaire seeking details of general health and with special reference to asthma and any other past or recent chest illness was completed. Roughly one week before the test the height of most of the children was measured by JNT at school using a Microtoise tape.⁸ On the day of the test the children were taken, one class at a time, by bus to a hospital gymnasium where the ambient temperature was 16–20°C and the relative humidity was 37–44%.⁹ The children were instructed not to exercise on the day of the test and to take their medications, if any, as usual. Children who did not have parental consent or who were unwilling to participate were excluded.

In the FRAST the children were instructed to run as quickly as possible for six minutes.¹⁰ Peak flow (PEFR, best of three efforts) was recorded for each child by OMB using a Wright peak flow meter immediately before the test and at 1, 5, and 10 minutes after the run. Heart rate during running was monitored in alternate children with a telemetric device whose characteristics have been described previously.¹¹ All children monitored exceeded a rate of 170/minute. The children ran in groups of nine to 12 at a time and were observed and encouraged by a school teacher who recorded their running time. Children had to complete at least five minutes' intense running to be acceptable.¹² Those showing evidence of bronchoconstriction at the end of the run were closely observed by a doctor (JNT).

Bronchospasm causing distress, which was severe or persisted for more than 10 minutes, was treated with bronchodilators. An abnormal response to the FRAST was defined as a reduction in the postexercise peak flow of more than 15% of the pre-exercise value on at least two occasions. Children who failed to complete the FRAST and who were not asthmatic nor had an obvious reason (for example, incoordination) were asked to repeat the test on another day.

Results

ANALYSIS OF QUESTIONNAIRE

Questionnaires were completed satisfactorily on all

Table 1 Age, sex, and asthma status of the 509 children asked to participate in the Free Running Asthma Screening Test

	Age (years)					
	6	7	8	9	10	11
<i>Boys</i>						
Total	12	53	46	49	37	64
With asthma	1	4	6	5	2	4
<i>Girls</i>						
Total	7	27	42	31	27	57
With asthma	0	4	2	3	1	3

509 children who made up the original sample. The question 'Does your child ever wheeze?' produced 52 positive answers. Of these, 36 (7%) children were deemed to be asthmatic because they also answered 'yes' to the question 'Has your child wheezed during the last 12 months?', and reported that they had 'wheezy bronchitis,' 'asthma,' or 'chestiness.'

ANALYSIS OF FRAST

The age and sex of the 509 children are shown in table 1. Parental consent was refused in three cases and three children were absent on the test day (fig 1). In the 503 tests performed, 69 children failed to complete the test of whom 14 were said to be asthmatic. In the remaining 55 failure to complete the test was explicable in 18 cases. Explanations included incoordination, ingrowing toe nails, arm in plaster, and wilful non-cooperation. When the remaining 37 children were retested their FRAST was normal.

There were 22 children said to be asthmatic among the 434 who completed the FRAST. Of these half had an abnormal response. Among the remaining 412 supposedly healthy children there were 14 abnormal FRAST tests. None of the 14 children with positive tests had had a recent upper respiratory tract infection. They had no symptoms but had abnormal signs when screened. Retrospective examination of the questionnaires of these 14 children

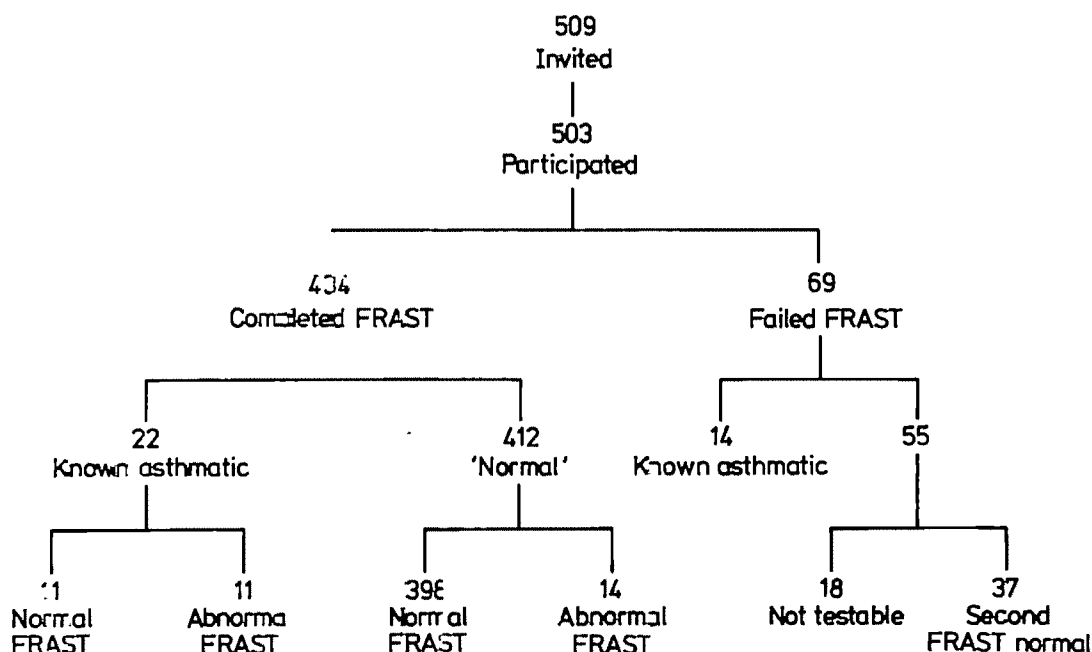


Fig 1 Response of the 509 school children who were invited to perform the Free Running Asthma Screening Test (FRAST).

confirmed that none had responded positively to asthma related questions, but three were reported as having had an allergy and two had relatives with asthma. The results of the 412 subjects were then analysed to determine how many tests would have been abnormal had a cut off point of 10% or 20% peak flow reduction been applied and the answers were 37 and 10, respectively

ANALYSIS OF PEAK FLOW BEFORE FRAST

In table 2 the mean PEFR of all 471 children whose height had also been measured is shown subdivided by sex and age. The linear regression equations relating PEFR to height (H) for (a) all children, (b) all children excluding asthmatics, and (c) all children excluding asthmatics and those with abnormal FRAST results were:

- (a) $PEFR = 4.1H - 286$ ($n=471$, $r=0.73$)
- (b) $PEFR = 4.1H - 291$ ($n=435$, $r=0.73$)
- (c) $PEFR = 4.1H - 296$ ($n=421$, $r=0.73$).

Using equation (a) the predicted PEFR for each child was calculated and then the actual PEFR was converted to a standard deviation score using the relevant PEFR standard deviation for age and sex. The mean standard deviation scores for all 471 children did not differ significantly from 0 (fig 2) and more importantly neither did the mean (SD) standard deviation score of the asthmatic children: -0.25 (0.96) nor that of the children with abnormal FRAST: $+0.12$ (1.04).

ANALYSIS OF PEAK FLOW AFTER FRAST

Detailed analysis of the postexercise PEFR in the 14 children with abnormal FRAST results showed that all had an abnormally low PEFR at 5 and 10 minutes but only five were abnormal 1 minute after exercise. Three required nebulised bronchodilator treatment between 5 and 10 minutes and eight more were given bronchodilators by inhaler after 10 minutes. There-

fore all these children would have been identified on either a 5 or a 10 minute PEFR alone. Ten of the 412 normal children, however, had an abnormal PEFR at 5 minutes and three others were abnormal at 10 minutes.

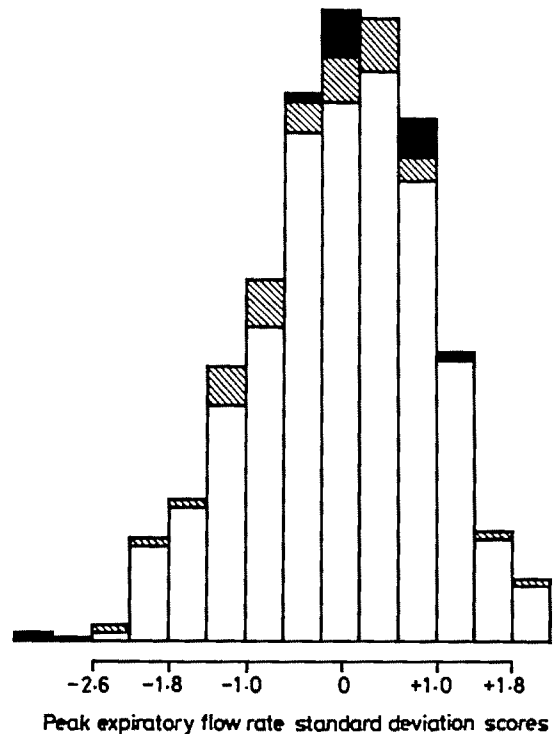


Fig 2 Distribution of peak expiratory flow rate results of 471 Sheffield children aged 6 to 12 years expressed as standard deviation scores. Children with an abnormal Free Running Asthma Screening Test response are indicated by black areas and known asthmatics by hatched areas

Table 2 Mean (SD) height and peak expiratory flow rate (PEFR) of 471 of the children who completed the Free Running Asthma Screening Test subdivided by age and sex

	6	7	8	Age (years) 9	10	11	12
	Boys						
Height (cm)	(n=12) 121.1 (6.0)	(n=54) 124.5 (6.0)	(n=44) 128.3 (5.8)	(n=47) 134.4 (6.1)	(n=37) 142.1 (5.4)	(n=66) 144.8 (7.1)	(n=8) 152.3 (9.4)
PEFR (1 minute)	207.5 (37.0)	221.3 (44.0)	224.5 (42.0)	271.1 (49.7)	299.3 (45.9)	307.9 (55.3)	338.7 (67.8)
	Girls						
Height (cm)	(n=7) 120.0 (5.4)	(n=26) 123.6 (7.4)	(n=44) 128.3 (6.0)	(n=30) 132.5 (4.8)	(n=27) 141.9 (5.6)	(n=59) 144.7 (6.3)	(n=10) 153.2 (6.4)
PEFR (1 minute)	199.2 (32.3)	218.2 (36.0)	231.1 (38.3)	240.0 (43.0)	311.8 (47.7)	308.8 (47.7)	355.0 (52.7)

Discussion

There is a need to identify children who may suffer from asthma but not know it. Most known asthmatic children have exercise induced bronchospasm¹³ and for this reason we studied the feasibility of screening children at school for exercise induced bronchospasm as a marker of childhood asthma and compared this with response to a parental questionnaire that has been shown previously to have good diagnostic precision.² The FRAST was created as a standardised test that can be performed in a normal school environment and which as a good chance of detecting unrecognised asthma.

In the present study the parents and school-teachers cooperated enthusiastically even though a national teaching dispute was in progress at the time. The drop out rate before the test was very low (1%). To ensure a standard environment all tests were performed in a hospital gymnasium, which meant bussing the children to and from school, but there is no reason why the test should not take place in the school gymnasium or assembly hall. The apparatus required is modest and only a clock timer, a peak flow meter, mouth pieces, and facilities for giving bronchodilator treatment are needed. Not fewer than three adults were present when the tests were performed: a school teacher, physiotherapist, and a doctor, and our experience indicates that this is the minimum needed to screen ethically and accurately.

The pattern of free running used in the FRAST ensured a high sustained submaximal workload as judged by heart rate monitoring in 240 of the 503 children tested.¹¹ The children with heart rate monitors could not be distinguished from the rest during exercise. The choice of 1, 5, and 10 minutes as the times for measuring PEFR after exercise was based on previous work.¹⁴ Examination of the results retrospectively showed that the discriminating power of the postexercise PEFR increased with time. The 1 minute PEFR result was useless in identifying children with exercise induced bronchospasm whereas the 5 and 10 minute PEFR results were both subnormal in every case. If the 5 minute PEFR result had been used alone, however, there would have been a 42% false positive rate and if the 10 minute PEFR result had been used alone there would have been a 18% false positive rate. Furthermore some of the previously unrecognised asthmatic children deteriorated between 5 and 10 minutes after exercise. Three needed nebulised bronchodilator treatment before 10 minutes and eight more required bronchodilator by inhaler after 10 minutes. For these reasons it is prudent to measure PEFR 5 and 10 minutes after exercise but

not at 1 minute, and it is essential that appropriate medical support is present.

The 503 children studied were subdivided on the basis of completing the test, known asthma, and response (fig 1). Asthmatics were included in the study group to avoid the potential of social stigma and to provide an indication of their quality of control. Only 11 of 36 asthmatics had a normal response, the remainder either completed the test and needed bronchodilator treatment or failed the test because of fear of bronchospasm. These results reflect the quality of medical management of known asthma and do not indicate poor discriminatory power of the FRAST. Among the 467 non-asthmatic children, 37 needed a second test before being shown to be normal and 18 (4%) were not testable. All 14 (3%) children with an abnormal FRAST result were studied further with the consent of their parents and family doctor and as a result 10 were diagnosed as asthmatic and were given appropriate treatment.

The relation between pretest PEFR and height in this sample differs from that reported for a similar cohort of Sheffield children studied recently.¹⁴ This may be because the present study was deliberately carried out in the pollen season (April-May) whereas the earlier study took place in December. When the PEFR of the present subjects was converted to standard deviation scores using the earlier standards¹⁵ the mean (SD) of the group was significantly less than 0: -0.35 (1.00) ($p < 0.001$). The possibility that PEFR of normal children changes with seasons of the year could be tested by studying a large cohort sequentially.

Any screening test for asthma is of necessity empirical and the FRAST shares with all other screening procedures the weakness that some unrecognised asthmatic child may have had a normal FRAST response. The usefulness of the FRAST approach, however, is shown by the fact that, with the definition of abnormal chosen by us, 10 out of 14 abnormal FRAST responders were subsequently diagnosed asthmatic. This produced a total of 46 (9%) asthmatic children in the whole sample and our questionnaire identified only 78% of these, not 96% as reported by others.² If the more modest definition of abnormality, 10% fall in postexercise PEFR, had been used there would still only have been 37 children requiring further investigation to confirm or exclude asthma. The importance of FRAST is further shown by the fact that only one of the 14 children might have been predicted from an abnormal pretest PEFR result.

If our results are representative of schoolchildren in general, roughly one child in every class has an unrecognised exercise induced bronchospasm and

deserves medical attention. We conclude that such children can be identified by the FRAST test, which can be carried out at any school with the cooperation of the teachers, school nurse, and school doctor.

We are grateful to Mrs M Pickering for technical help, to the Sheffield Asthma Society for financial support (OMB), and to staff, pupils, and their parents of the Hunters Bar First and Middle Schools and Marcliffe School who cooperated in this study

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Tuberculosis in children: a national survey of notifications in England and Wales in 1983

MEDICAL RESEARCH COUNCIL TUBERCULOSIS AND CHEST DISEASES UNIT

SUMMARY A survey of all notifications of tuberculosis in children (aged less than 15 years) in England and Wales in 1983 showed a decline of 35% in the estimated annual number of previously untreated children notified since the previous survey in 1978-9. Of the 452 children in the 1983 survey, 217 (48%) were of white, 79 (17%) of Indian, and 104 (23%) of Pakistani or Bangladeshi ethnic origin. The decline in the number of Indian children notified (46%) was much greater than that for Pakistani and Bangladeshi children (16%). In both surveys the estimated annual notification rate was much higher for the Indian and the Pakistani and Bangladeshi ethnic groups (32 and 52/100 000, respectively in 1983) than for the white group (2.4/100 000 in 1983). The mean annual decline in rate between the two surveys was 14% for the Indian, 10% for the Pakistani and Bangladeshi, and 7% for the white children. In both surveys the rates for the children of Indian subcontinent (Indian, Pakistani, and Bangladeshi) ethnic origin born in the United Kingdom were considerably lower than for those born abroad. Of the 452 children in the 1983 survey, 342 (76%) had respiratory disease (including 26 (6%) with a non-respiratory lesion as well). Less than half (134, 45%) had a pulmonary lesion at independent assessment of chest radiographs, a further 115 (38%) had only enlarged intrathoracic nodes. Only 60 (19%) of the children with respiratory disease only had a positive culture from a respiratory specimen, but the culture positivity rate in those tested was 45%. Almost two thirds of the children with non-respiratory disease had lesions of the extrathoracic nodes, nearly all cervical. There were 20 children with tuberculosis meningitis in the 12 months, including 12 (6%) of the 217 white and six (3%) of the 183 children of Indian subcontinent ethnic origin.

In a survey of all notifications of tuberculosis in England and Wales for a six month period in 1978/9 nearly 10% of newly notified previously untreated cases were children (aged less than 15 years).¹ The survey provided information that is not available from the official published figures for notifications on the ethnic origin and the characteristics of disease, in particular the bacteriological and radiographic characteristics of respiratory disease.² It also showed that 23% of the official published total of notifications were, in fact, for children who were not suffering from tuberculosis but were being given chemoprophylaxis. As a result of the survey it was recommended that cases of chemoprophylaxis should be identified separately from those with disease in the returns to the Office of Population Censuses and Surveys (OPCS) so that they are not included in the official tuberculosis statistics.³

Half the children with tuberculosis in the 1978/9 survey were of non-white ethnic origin, with over a third being of Indian subcontinent (Indian, Pakis-

tani, or Bangladeshi) ethnic origin. The children of Indian subcontinent ethnic origin, both those born abroad and those born in the United Kingdom, had much higher annual notification rates than the white children.

A second national survey was undertaken in 1983, for the whole 12 months, to obtain more information on childhood tuberculosis and in particular more accurate estimates of the notification rates in the different ethnic groups.⁴ A follow up of the children with respiratory disease and those with extrathoracic lymph node lesions was undertaken two years after the last child was notified. This report describes the characteristics at the time of notification and compares the findings with those of the 1978/9 survey.

Methods

During the 12 month survey period (week ending 7 January to week ending 30 December 1983) a

photocopy of every tuberculosis notification form received by each of the 403 authorities in England and Wales and reported to the OPCS was sent to the Tuberculosis and Chest Diseases Unit (TCDU) by the Medical Officer for Environmental Health. The OPCS provided the TCDU with information on the notifications reported to them weekly by the medical officers for environmental health so that the unit could check that photocopies of all the notifications had been received. All clinicians who notified children (aged less than 15 years) were asked to complete a specially designed patient form for each, and to provide a pretreatment posteroanterior chest radiograph for independent assessment for all children with respiratory disease (defined to include a lung lesion, a pleural effusion, or mediastinal lymphadenopathy). The patient forms were matched in the TCDU with the photocopies of the notification forms to confirm that no child had been overlooked.

Information on the patient form included (a) race or ethnic group/descent, which was classified as one of the following: white, West Indian, African, Indian, Pakistani, Bangladeshi, Arab, Chinese, or other (including mixed descent); (b) for patients born abroad the country of birth and year of first entry to the United Kingdom; (c) the site(s) of disease; (d) date that chemotherapy was started; (e) results of bacteriological and histological examinations (if no positive culture results were recorded, a further enquiry was made four months after the date of notification); and (f) whether the patient had ever been treated for tuberculosis previously.

The results of sensitivity tests to antituberculosis drugs given in this report are restricted to those from the six regional centres for tuberculosis bacteriology and the Mycobacterium Reference Unit of the Public Health Laboratory Service (PHLS) which use standard techniques and definitions. The Communicable Disease Surveillance Centre of the PHLS coordinated their contribution to the survey.

Results

During the 12 months of the survey the TCDU received details of 788 notifications for children and systematic checks against the OPCS information confirmed that every notification in England and Wales during the year for this age group was included. In order to restrict the analysis to newly notified previously untreated patients with tuberculous disease several categories of notifications were excluded by the TCDU (table 1).

Of the 788 notifications in the 12 months, 336 (43%) were excluded; this was mainly because the children were receiving chemoprophylaxis (247,

31%). Of these, 222 patients (28%) were excluded on the basis of information available from the notification survey, a similar proportion to the 1978/9 survey (26%). There were 21 children with BCG abscesses notified in 1983 but none in 1978/9.

Of the 50 children in 1983 in whom the diagnosis was changed subsequently, 24 had disease due to mycobacteria other than *Mycobacterium tuberculosis*, a much higher proportion than in the 1978/9 survey. (These are very unlikely to be the total number of patients with disease due to mycobacteria other than *M. tuberculosis* diagnosed in the survey periods as there is no statutory requirement to notify them³). All 24 children excluded from the main analysis for this reason had lymph node lesions; 19 were of white, two of Indian subcontinent, and one of African ethnic origin; for the remaining two children the ethnic origin was not known. In all except one child the cervical nodes were affected. *M. avium intracellulare* was isolated from 17, and *M. malmoense* from two patients. For four of the remaining five children a skin test with avian purified protein derivative was positive but *M. avium intracellulare* was not isolated.

There were, in all, 452 newly notified, previously untreated patients in the 12 months of 1983. To make comparisons with data from the 1978/9 survey, however, the exclusions that were based on information only available at the time of the follow up have been disregarded, the figures for the comparisons

Table 1 Notifications for children in the 1983 and 1978/9 surveys

	1983 (12 months) No (%)	1978/9 (six months) No (%)
Notifications to medical officers for environmental health in survey period	788 (100)	512 (100)
Duplicate notifications removed by the Tuberculosis and Chest Diseases Unit	14 (2)	3 (1)
Children receiving chemoprophylaxis	247 (31)	135 (26)
Children with BCG abscess	21 (3)	0
Children in whom diagnosis was changed		
Disease due to mycobacteria other than <i>M. tuberculosis</i>	24 (3)	4 (1)
Other non-tuberculous disease	26 (3)	9 (2)
Children who had previous treatment for tuberculosis	4 (1)	8 (2)
Newly notified previously untreated patients	452 (57)	353 (69)
Corrected OPCS total of notifications	617 —	479 —

being 353 patients notified in a six month period in 1978/9 and 486 in a 12 month period in 1983.

COMPARISON WITH OPCS PUBLISHED FIGURES

In 1983 the corrected OPCS figure (617) was 37% higher than the TCDU figure (452), but only 27% higher if based on information available at the time of the notification survey. The corresponding figure for 1978/9 was 36%. The small number of children who had had previous treatment should have been included in the OPCS totals but a considerable proportion of the children in the other groups in table 1 must also have been included. The largest group was the children receiving chemoprophylaxis, in 1978/9 the evidence is that 112 (83%) of the 135 cases of chemoprophylaxis were included as cases of tuberculosis in the returns to the OPCS. This represents 23% of the 479 notifications of tuberculosis, but in 1983 only 65 (29%) of the 222 cases of chemoprophylaxis (known at the time of the notification survey) were included, representing 11% of the 617 notifications in the 12 months. This difference was likely to be due to recommendations to clinicians and medical officers for environmental health³ and changes in the OPCS reporting procedure⁵ aimed at separating chemoprophylaxis cases from cases of tuberculous disease.

DOCTORS NOTIFYING CASES OF TUBERCULOSIS

Most (265, 59%) of the 452 cases of tuberculosis in children were notified by chest physicians, 151 (33%) by paediatricians, and the remaining 36 (8%) from other specialities. In contrast, in 1978/9 the proportion notified by chest physicians was 73% and only 15% were notified by paediatricians.

ETHNIC ORIGIN

Of the 452 children, 48% were of white, 40% of Indian subcontinent, and 4% of West Indian ethnic

origin; all other ethnic groups together contributed only 7% of the notified cases (table 2). (The findings were very similar in the 1978/9 survey.) In 1983, there were seven children of Chinese, four of African, two of Arab, two of Vietnamese, and one of Malaysian ethnic origin. A further 17 children were of mixed ethnic origin, 13 being of white and West Indian parentage.

The number of white children notified annually had declined by 35% in the four and a half year period between the midpoint of the surveys (based on an annual estimate for 1978/9 that took into account seasonal variation in the notifications), the corresponding declines for the Indian and the Pakistani and Bangladeshi children being 46% and 16%, respectively. Thus whereas there were more children of Indian than of Pakistani or Bangladeshi ethnic origin notified in 1978/9, the position was reversed in 1983 (table 2).

TYPE OF DISEASE

Respiratory disease only was present in 316 (70%) of the 452 children, non-respiratory disease only in 110 (24%), and both in 26 (6%). The corresponding proportions for the 217 white children were 145 (67%), 64 (29%), and 8 (4%), respectively, and for the 133 children of Indian subcontinent ethnic origin, 132 (72%), 36 (20%), and 15 (8%), respectively. The findings were broadly similar in the 1978/9 survey.

ESTIMATED ANNUAL NOTIFICATION RATES

Population figures by ethnic group for 1978/9 were derived from the 1978 National Dwelling and Housing Survey (NDHS),⁶ and for 1983 from the 1983 Labour Force Survey (LFS) (OPCS unpublished findings). As the NDHS did not include Wales, estimated annual rates have been calculated for England only both for 1978/9 and 1983.

Table 2 *Ethnic origin and type of disease*

Ethnic group	1983 survey (12 months)				Total for 1978/9 (six months) No (%)
	Respiratory disease only* No (%)	Non-respiratory disease only No (%)	Both No (%)	Total No (%)	
White	145 (44)	64 (58)	8 (31)	217 (48)	176 (50)
Indian	57 (42)	15 (14)	7 (27)	79 (17)	74 (21)
Pakistani or Bangladeshi	75 (24)	21 (19)	8 (31)	104 (23)	61 (17)
West Indian	17 (5)	2 (2)	0 (0)	19 (4)	18 (5)
Other	22 (7)	8 (7)	3 (12)	33 (7)	24 (7)
Total	316 (100)	110 (100)	26 (100)	452 (100)	353 (100)

*Includes children with a pulmonary lesion, a pleural effusion, or intrathoracic nodes or any combination of the three.

†Includes three patients whose ethnic origin was not known.

Comparisons of the 1978 and 1983 population estimates showed important discrepancies of the order of 30% for children of the Indian and the Pakistani and Bangladeshi ethnic groups.⁷ Revised estimates for the 1978 population, based on the 1983 LFS (OPCS unpublished findings), and hence revised notification rates, have been calculated for these ethnic groups.⁷

In order to calculate the best estimates of the rates in 1983, the revised population, based on information from both the notification survey and follow up has been used (namely, a total of 452 patients, 217 of white and 183 of Indian subcontinent ethnic origin). To make comparisons with the 1978/9 survey for which no follow up was undertaken, however, figures based on the data available at the time of the notification survey in 1983 are also provided.

In 1983 the highest rates occurred in the children of Indian subcontinent ethnic origin (table 3), 32/100 000 for the Indian and 52/100 000 for the Pakistani and Bangladeshi group, much higher than for the white children (2.4). The rates for the other non-white ethnic groups were also substantially higher than for the white group. The rate for the West Indian group was 17/100 000, but the true rate is likely to be lower because there is evidence that the population was underestimated (OPCS, personal communication). The estimated annual rate had dropped in the main ethnic groups between the

two surveys, the average annual decline being 7% for the white, 16% for the Indian, and 12% for the Pakistani and Bangladeshi children in the four and a half year period between the midpoint of the surveys. After standardising the rates for the Indian subcontinent ethnic groups for both survey years to a common reference population (because of differences in the characteristics of the populations⁷), however, the average annual declines were 14% for the Indian and 10% for the Pakistani and Bangladeshi ethnic groups.

The rates per 100 000 for the white children and for the children of Indian subcontinent origin, according to whether the latter were born in the United Kingdom or abroad, are shown in table 4. In 1983 the rates for the children (of all ages) of Indian and of Pakistani and Bangladeshi ethnic origin born in the United Kingdom (27 and 48, respectively) were lower than for those born abroad (62 and 63, respectively) but were still much higher than the white rate (2.4). The rate for the Indian and the Pakistani and Bangladeshi children born in the United Kingdom within the five years before the survey (that is, those aged 0-4 years at notification) who must have been recently infected, was 10 times as high as for the corresponding group of white children in 1983, indicating that the infants and young children of Indian subcontinent ethnic origin were exposed to a high risk of infection within their community.

Table 3 *Estimated annual notification rates of newly notified previously untreated children per 100 000 population of England for 1983 and 1978/9. (Figures in brackets are based on the data available at the time of the notification survey only)*

Ethnic origin	1983 Survey								1978/9 Survey				
	Population estimate for children under 15 years* (thousands)	All cases			All respiratory† disease		All non-respiratory disease		Population estimate for children under 15 years* (thousands)	All cases			
		No of patients in 12 months	Annual rate per 100 000	Ratio to white rate	Annual rate per 100 000	Ratio to white rate	Annual rate per 100 000	Ratio to white rate		No of patients in six months†	Annual rate per 100 000	Ratio to white rate	
White	8348	201 (221)	2.4 (2.6)	—	1.7	—	0.8	—	9516	164	3.6	—	
Indian	250	79 (85)	32 (34)	13	26	15	9	12	211	74	74	20	
Pakistani or Bangladeshi	195	101 (105)	52 (54)	21	41	24	15	20	138	60	92	25	
West Indian	110	19	17 (17)	7	15	9	2	2	181	18	21	6	
Other	212	32	15 (15)	6	11	7	5	7	159	20	27	7	
Total for England	9116	432 (462)	4.7 (5.1)	—	3.6	—	1.4	—	10 205	339	7.0	—	

*Both the estimate for 1978/9 and for 1983 include 254 000 children in each survey for whom the ethnic origin was not clearly stated, these have been distributed proportionately among those for whom the ethnic origin was known. The 1978/9 estimate for the Indian and the Pakistani and Bangladeshi ethnic groups was derived from the 1983 data (see above).

†For three patients in 1978/9 included in the total the ethnic origin was not known.

‡Defined as a pulmonary lesion or intrathoracic lymph node disease or a pleural effusion or any combination of these.

Table 4 *Estimated annual notification rates per 100 000 population for children of white and Indian subcontinent ethnic origin in England for 1983 and 1978/9. Rates in brackets are based on estimated populations of less than 10 000*

Age (years)		White		Indian				Pakistani/Bangladeshi			
		1983	1978/9	Born in the United Kingdom		Born abroad		Born in the United Kingdom		Born abroad	
				1983	1978/9	1983	1978/9	1983	1978/9	1983	1978/9
0-4	Population*	2636	2550	95	77	2	4	71	44	6	8
	Cases†	73	43	23	17	1	0	29	12	5	7
	Rate per 100 000	2.3	3.6	24	47	(42)	(0)	41	58	(82)	(176)
5-9	Population*	2511	3319	73	57	8	13	39	37	21	16
	Cases†	59	74	12	15	2	9	18	10	11	7
	Rate per 100 000	2.3	4.7	16	56	(25)	142	46	58	54	92
10-14	Population*	3201	3637	54	33	17	26	36	18	23	15
	Cases†	69	47	26	15	14	18	23	9	15	15
	Rate per 100 000	2.2	2.7	48	96	82	146	63	106	67	211
All ages	Population*	3343	9516	223	167	27	44	146	98	49	40
	Cases†	201	164	61	47	17	27	70	31	31	29
	Rate per 100 000	2.4	3.6	27	60	62	130	48	67	63	155
	Rate per 100 000 based on notification survey data only for 1983	2.6	—	29	—	70	—	50	—	65	—

*In thousands; 1978/9 figures based on 1983 population.

†In six month period for 1978/9 and the whole year for 1983.

As most (38%) of the children were of white or Indian subcontinent ethnic origin, the rest of the report concentrates on the findings for these ethnic groups.

RESPIRATORY DISEASE

Radiographic assessments

A posteroanterior chest radiograph, taken within the period from six weeks before to four weeks after the start of chemotherapy, was available for 301 (88%) of the 342 children with respiratory disease (table 5). A 50% random sample of the radiographs from the 1978/9 survey, stratified by ethnic origin, was drawn and the films from both surveys were masked and mixed and then read by the independent assessor (MC), who was unaware of which survey any patient was from. The assessments of the 1973/9 films were broadly similar to the original reading for the full population of the 1978/9 films (by a different assessor). The proportion reported to have enlarged intrathoracic nodes only was higher (37%), however, than that reported previously (26%), and the proportion classified as within normal limits was lower, 11% compared with 19%.

In 1983, the radiographs of 31 (10%) children were considered at independent assessment to be within normal limits, the proportion being higher for the white children (13%) than for the children of Indian subcontinent ethnic origin (7%). Of these 31

children, three had non-respiratory lesions and two had a positive smear (but negative culture); one from pleural fluid and the other from a gastric aspirate. For most of the remainder the clinician (who often had other radiographs available) commented that there was a radiographic abnormality (a pulmonary lesion in 10 children, enlarged hilar nodes in 10, and a primary complex in three).

A pulmonary lesion was reported on 134 (45%) of the radiographs (100 having enlarged nodes as well) and enlarged nodes only were seen on a further 115 (38%). Of the 134 children with a pulmonary lesion, most (96, 72%) had small lesions of up to a total area of one sixth of a lung field, but 24 children had lesions of a total area of more than one third of a lung field (including nine with miliary disease), the proportion being higher in the Indian subcontinent ethnic group (14 of 62) compared with the white group (six of 57). Obvious cavitation on a single posteroanterior film was present in seven children, three of whom were white and three of Indian subcontinent ethnic origin.

The findings were broadly similar in the 1978/9 survey for all ethnic groups combined (table 5) and for the main ethnic groups (data not tabulated here).

Bacteriological results

Of the 316 children with respiratory disease only 60

(19%) had a positive culture from a respiratory specimen (20 sputum, 33 gastric aspirate, two pleural aspirate, three bronchial aspirate, one bronchial biopsy, and one mediastinal node), 27 (9%) children had a positive smear as well (11 sputum, 13 gastric aspirate, two bronchial aspirate, and one mediastinal node) (table 6). The findings were similar for the children of white and Indian subcontinent origin. Although cultures were obtained from only 133 children, the positivity rate for those with a culture was 45%. The findings in the 1978/9 survey were similar.

It is of interest that of the 113 children aged less than 5 years, 25 (22%) had a positive culture from respiratory specimens compared with 14 (15%) of the 91 children aged 5 to 9 years and 21 (19%) of the 112 aged 10 to 14 years; eight, six, and 11, respectively having positive smears.

A sensitivity test result from a reference laboratory was available for 47 (including 22 white and 18 of Indian subcontinent ethnic origin) children with respiratory disease, and all except four of the strains were fully drug sensitive. Of the four, two were resistant to streptomycin alone, one to isoniazid

Table 5 *Independent assessment of posteroanterior chest radiographs in children with respiratory disease for the two main ethnic groups and for all ethnic groups for 1983 and for all ethnic groups for 1978/9*

Radiographic assessment	1983 survey (12 months)			1978/9 survey (six months)
	All ethnic groups No (%)	White No (%)	Indian subcontinent No (%)	All ethnic groups No (%)
Pulmonary lesion*	134 (45)	57 (44)	62 (47)	56 (47)
Enlarged nodes only	115 (38)	47 (36)	53 (40)	44 (37)
Effusion only	12 (4)	7 (5)	4 (3)	2 (2)
Enlarged nodes and effusion	9 (3)	3 (2)	5 (4)	3 (3)
Calcification only	0	0	0	1 (1)
Within normal limits	31 (10)	17 (13)	9 (7)	13 (11)
Total patients assessed	301 (100)	131 (100)	133 (100)	119 (100)
Extent of pulmonary disease				
Miliary	9 (7)	4 (7)	3 (5)	6 (11)
> One lung (three zones)	5 (4)	0	5 (8)	1 (2)
One lung (three zones)	10 (7)	2 (4)	6 (10)	5 (9)
One third lung (one zone)	14 (10)	7 (12)	6 (10)	2 (4)
< One sixth lung (half zone)	96 (72)	44 (77)	42 (68)	42 (75)
Obvious cavitation	7 (5)	3 (5)	3 (5)	2 (4)
Total patients with a pulmonary lesion	134 (100)	57 (100)	62 (100)	56 (100)

*Enlarged thoracic nodes were also present in 100 children (39 white, 48 Indian subcontinent) in 1983 and 43 in 1978/9

Table 6 *Results of smear and culture examination in children with respiratory disease only for the two main ethnic groups and all ethnic groups for 1983 and for all ethnic groups for 1978/9*

Bacteriological result	1983 survey (12 months)			1978/9 survey (six months)
	All ethnic groups No (%)	White No (%)	Indian subcontinent No (%)	All ethnic groups No (%)
Culture positive				
Smear positive	27 (9)	13 (9)	10 (8)	14 (6)
Smear negative	27 (9)	9 (6)	12 (9)	15 (6)
No smear result	6 (2)	2 (1)	3 (2)	5 (2)
Culture negative	73 (23)	35 (24)	33 (25)	53 (22)
No culture result	183 (58)	86 (59)	74 (56)	153 (64)
Total patients assessed	316 (100)	145 (100)	132 (100)	240 (100)

alone, and one to both drugs, three of the patients being of Indian subcontinent and the fourth (with resistance to streptomycin alone) of white ethnic origin. No strain was resistant to rifampicin or ethambutol. All except one of the 47 strains were identified as *M. tuberculosis*; the remaining strain from a Chinese child was identified as *M. bovis*.

NON-RESPIRATORY DISEASE

Clinical characteristics

In the report of the 1978/9 survey the nine white children with erythema nodosum and one Chinese child with erythema induratum were included with those with cutaneous tuberculosis and therefore classified as non-respiratory disease. The 10 (all white) children with erythema nodosum in the 1983 survey were classified according to the site of the tuberculous lesion and therefore for comparisons between the surveys the 1978/9 data have been re-analysed in the same way.

Of the 136 children with non-respiratory lesions in the 1983 survey the extrathoracic lymph nodes were affected in 85 (61%) (table 7). In most of these children (73, 88%) cervical nodes were affected, the remainder being axillary (5.6%), or inguinal (5.6%). In 1983 43 (67%) white and 27 (53%) children of Indian subcontinent ethnic origin with non-respiratory disease had lymph nodes affected; in 1978/9 the numbers were 18 (37%) and 36 (71%), respectively. The number of children of Indian subcontinent ethnic origin with lymph node disease declined by 62% between the surveys, but the number of white children increased by 37%. The annual notification

rate for lymph node disease for the children of Indian subcontinent ethnic origin fell from 22/100 000 in 1975/6 to seven in 1983, but increased from 0.4 to 0.6/100 000 for the white children.

The only other lesions affecting more than 10% of the children with non-respiratory lesions were meningitis (15%) and bone or joint lesions (14%). Tuberculous meningitis occurred in 12 (17%) of the 72 white and six (12%) of the 51 children of Indian subcontinent ethnic origin, whereas in the 1978/9 survey, 12 (30%) of the 40 white but only one (2%) of the 51 children of Indian subcontinent ethnic origin were affected (in six months). Fifteen of the total of 20 children with meningitis in 1983 were aged less than 5 years at the time of diagnosis, six (five of them white) less than 2 years.

Bone or joint disease occurred in five (7%) of the 72 white and 12 (24%) of the 51 children of Indian subcontinent ethnic origin with non-respiratory lesions in 1983, the corresponding proportions for 1978/9 were three (8%) of 40 and seven (14%) of 51 children (in six months). The spine was affected in nine of the 19 children with a bone or joint lesion in 1983 (including two white and six children of Indian subcontinent ethnic origin) and the hip in three (one white, two Indian subcontinent). In four children of Indian subcontinent ethnic origin the bones of the hand were affected.

Bacteriological and histological findings

Of the 83 children with lymph node tuberculosis in 1983, 39 had a culture result from a node and only eight (21%) were positive: one of 25 from white children and seven of 11 children of Indian subcontinent ethnic origin. In 50 of the 52 children with a histological result from the node the findings were compatible with a diagnosis of tuberculosis. In all, 37 (77%) of the 48 white and 14 (52%) of the 27 children of Indian subcontinent ethnic origin had bacteriological or histological confirmation of the diagnosis of tuberculosis either from the lymph node or from another site.

A culture result from the cerebrospinal fluid was obtained for 18 (including 11 white and five children of Indian subcontinent ethnic origin) of the 20 children with meningitis and 10 (including seven white and two children of Indian subcontinent ethnic origin) were positive. A smear result was obtained for 19, of which seven were positive (five confirmed on culture, the sixth negative, and no culture result available for the seventh child). Of the eight children without a positive smear or culture from the cerebrospinal fluid, two had bacteriological or histological confirmation from another site and three had radiographic evidence of respiratory disease.

Table 7 *Sites of non-respiratory disease in children with or without a respiratory lesion for the two main ethnic groups and all ethnic groups for 1983 and all ethnic groups for 1978/9*

Site	1983 survey (12 months)			1978/9 survey (six months)
	All ethnic groups No (%)	White No (%)	Indian subcontinent No (%)	All ethnic groups No (%)
Extrathoracic lymph nodes	23 (61)	48 (67)	27 (53)	62 (60)
Meninges	20 (15)	12 (17)	6 (12)	14 (14)
Bone or joint	9 (14)	5 (7)	12 (24)	12 (12)
Abdomen	8 (6)	3 (4)	4 (8)	5 (5)
Miliary	4 (3)	3 (4)	0	5 (5)
Abscesses	1 (1)	1 (1)	0	5 (5)
Cutaneous	1 (1)	1 (1)	0	2 (2)
Other sites	5 (4)	2 (3)	2 (4)	6 (6)
Total patients	126 (100)	72 (100)	51 (100)	103 (100)

Five children had more than one non-respiratory lesion

Seven (including three white and three children of Indian subcontinent ethnic origin) of the 19 children with a bone or joint lesion had a positive culture from a biopsy specimen or pus, a further white child had histological confirmation of the diagnosis.

Sensitivity test results to isoniazid, rifampicin, ethambutol, and streptomycin were available for 22 (10 white, 10 Indian subcontinent, one Chinese, and one Vietnamese) of the 136 children with non-respiratory disease and all except two were fully sensitive. One Pakistani child with lymph node disease had a strain resistant to isoniazid alone, and one Chinese child with meningitis had a strain resistant to streptomycin.

ADDITIONAL INFORMATION ON THE PATIENTS IN THE 1983 SURVEY OBTAINED FROM THE FOLLOW UP SURVEY

For 313 children with respiratory disease, 65 with extrathoracic lymph node disease, and 15 with both (included subsequently with the lymph node group) additional pretreatment information was collected at the follow up survey.

Basis of diagnosis

The clinician reported that the diagnosis was made on the basis of bacteriological findings (with or without other evidence) in 16% of the patients, the numbers being 47 (15%) for the 313 with respiratory disease and 14 (18%) for the 80 with extrathoracic lymph node disease. In 246 (79%) of those with respiratory disease, the diagnosis was based on radiographic evidence and in 40 (50%) of those with extrathoracic lymph node disease on histological evidence (with or without other evidence). In the remaining 40 children it was based on clinical evidence in 36 (with tuberculin test findings in 27 and a history of contact in 33) and in four it was made on the basis of contact history only.

History of BCG vaccination

Of the 393 patients, 81 (21%) were known to have had BCG vaccination, and for 24 (6%) it was not known whether or not they had been vaccinated. The number vaccinated was higher for those with respiratory disease than for those with lymph node disease, 70 (24%) and 11 (15%), respectively of those in whom the history was known. A much higher proportion of the children of Indian subcontinent ethnic origin were known to have been vaccinated, 49 (43%) of those born in the United Kingdom and eight (21%) of those born abroad compared with only 16 (8%) of the white children. Of those vaccinated, 35 (71%) of the 49 children of Indian subcontinent ethnic origin born in the United Kingdom and six (38%) of the 16 white children were known to have been vaccinated in the first year of life.

History of contact

In all, 176 (45%) of the children were reported to have been diagnosed through contact tracing. In 82 the contact was the mother or father, in 18 a grandparent, in 23 a sister or brother, in 20 an aunt or uncle, and in 13 more than one family member. In two children the contact was a teacher, in 10 a friend, and in one a neighbour. For the remaining seven it was a casual contact (four) or the relationship was not known (three).

Discussion

Childhood tuberculosis remains important for several reasons. Infection with the tubercle bacillus in the youngest age groups must be relatively recent; it is therefore an indicator of continuing transmission of infection in the community. Further, serious and sometimes fatal forms of the disease such as meningitis and miliary disease may follow a primary infection and some forms—for example, meningitis and bone or joint disease—may leave permanent sequelae. Young children are not routinely protected by neonatal BCG vaccination in the United Kingdom. Neonatal vaccination has been recommended by the Department of Health and Social Security (DHSS), however, for infants of immigrant communities with a high incidence of tuberculosis.^{8,9} The BCG vaccination programme in schools currently offers protection to children of all ethnic groups aged 11–13 years but is likely to be withdrawn within the next five years. The need for children of Indian subcontinent ethnic origin and of other ethnic groups with a high incidence of tuberculosis to continue to receive BCG at birth or as soon as possible thereafter will continue.

Over the four and a half years between the midpoints of the surveys conducted by the Medical Research Council in 1978/9 and 1983, the estimated annual number of children notified declined by 35%. The declines were 35% for the white, 46% for the Indian, but only 16% for the Pakistani and Bangladeshi ethnic groups. An interesting difference between the ethnic groups was that the decline between the surveys in the total number of children with non-respiratory disease (that is, non-respiratory with or without respiratory disease as well) was much greater for the Indian subcontinent group, (51% compared with 27% for the white group) but the decline in respiratory disease was less (25% compared with 43%, respectively).

The estimated annual notification rates per 100 000 of the population aged less than 15 years declined in the main ethnic groups in the four and a half years between the surveys, the average annual decline being 7% for the white, 14% for the Indian, and 10% for the Pakistani and Bangladeshi ethnic

group. As in 1978/9 the rates for the children of Indian subcontinent ethnic origin born abroad were higher than those born in the United Kingdom, particularly for children of the Indian ethnic group, but even the rates for those children born in the United Kingdom were much higher than those for the white children. The proportion of children of Indian ethnic origin born in the United Kingdom was much higher in 1983 than in 1978/9 both in the proportion of patients (77%) and in the population of children from which they were drawn (89%) (compared with 64% and 75% respectively for 1978/9). The corresponding figures for the Pakistani and Bangladeshi ethnic group were 70% and 75% for 1983 and 52% and 71% for 1978/9. As immigration declines and an increasing proportion of the population of children of Indian subcontinent ethnic origin is born in the United Kingdom it is likely that the notification rates will continue to decline, but it is unlikely that they will approach the rates for the white children rapidly. Hence, further surveys will be important to monitor the changes. Children born to parents of Indian subcontinent ethnic origin in the United Kingdom are exposed to a much higher risk of infection here than are the white children and this risk may be increased by visits to their parents' country of origin¹⁰ or visits to this country by their relatives. A policy of BCG vaccination at birth, as recommended by the DHSS^{8,9} and the Joint Tuberculosis Committee of the British Thoracic Society,¹¹ will continue to be important for the foreseeable future. Although the recently reported trial of BCG vaccination in India has cast doubts on its efficacy in the study area of Madras State, the World Health Organisation still recommends the use of BCG vaccination 'as early in life as possible' where there is a high prevalence of tuberculosis, and in countries with a low prevalence that 'current BCG policies should continue to be adapted to the changing situation, taking into account both local and global epidemiological trends, including such factors as migration'.¹² In the United Kingdom the high level of protection achieved by BCG vaccination of schoolchildren was originally shown by the Medical Research Council trial,¹³ and the level of protection achieved at ages 15-24 years in 1933 by the schools' routine BCG programme was estimated to be 75%.¹⁴ There is also some evidence that BCG vaccination at birth affords protection against tuberculosis for children of both white and Indian subcontinent ethnic origin in the United Kingdom.¹⁵ The most important control measure, however, remains the early detection and adequate treatment of all cases of tuberculosis, particularly the cases of smear positive pulmonary disease in adults, the most infectious group.¹⁶

The distinction between chemotherapy for active disease and chemoprophylaxis is often blurred in children because of the difficulties in diagnosis. In order to try to clarify the issue for the purposes of notification, the Joint Tuberculosis Committee of the British Thoracic Society has defined chemoprophylaxis as 'the administration of one or more antituberculosis drugs to an individual, whether tuberculin negative or positive, without clinical, radiographic, or bacteriological evidence of tuberculous disease' and has recommended that if such individuals are reported to the medical officer for environmental health a letter is used and not a standard notification form.³ In addition, modifications have been made to the reporting system from the medical officer for environmental health to the OPCS so that cases of chemoprophylaxis can be separated from cases of tuberculosis.⁵ The proportion of cases included in the published OPCS figure that were found by the TCDU (often after a special enquiry to the clinician in charge) to be receiving chemoprophylaxis dropped from 23% in 1978/9 to 11% in 1983. Thus the number of cases of tuberculosis reported in 1983 is still exaggerated by the inclusion of cases of chemoprophylaxis but the proportion has dropped considerably since 1978/9. Neither survey gives a measure of the total number of children receiving chemoprophylaxis as many clinicians do not report them to the medical officer for environmental health because there is no statutory requirement that they should do so.

Respiratory disease was usually characterised by small pulmonary lesions or enlarged intrathoracic lymph nodes or both. As in 1978/9, however, there were a number of children with large pulmonary lesions, and indeed the group of Indian subcontinent ethnic origin had, on average, more extensive disease than the white group; three white and three children of Indian subcontinent ethnic origin having obvious cavitation on a posteroanterior film at independent assessment. These findings are in marked contrast to the adults where the white patients had, on average, more extensive lesions than the patients of Indian subcontinent ethnic origin. Bacteriological confirmation on culture of a respiratory specimen was obtained from 19% of the children with respiratory disease, compared with 14% in 1978/9. A particularly interesting finding was that the proportion with a positive culture was highest in the youngest (0-4 year) age group. Although less than half the children (of all ages) had a specimen examined, 45% of those with a culture result were positive, suggesting that bacteriological confirmation might well be obtained more often if special efforts are made to collect specimens.

Extrathoracic lymph node disease was the com-

monest form of non-respiratory tuberculosis in both the white children and those of Indian subcontinent ethnic origin in both surveys. Whereas the number of children with lymph node disease had declined by 62% in the group of Indian subcontinent ethnic origin at the second survey and the annual notification rate had declined, there was an increase of 37% in the number of such lesions in the white group representing an increase in the annual notification rate from 0.4 to 0.6/100 000. Confirmation of the diagnosis bacteriologically was obtained in only one of the 48 white children and seven of the 27 children of Indian subcontinent ethnic origin, but histological findings were reported as positive in 36 and 10, respectively. Some of the cases notified as cases of lymph node tuberculosis without bacteriological confirmation might have been due to other mycobacteria, especially in the white population. The number of children reported to have lymph node disease due to a mycobacterium other than *M. tuberculosis* increased from four patients in six months in the 1978/9 survey to 24 in 12 months in 1983; 19 of the 24 were white children with lymph node disease. This is certain to be an underestimate of the number of patients with disease due to other mycobacteria as there is no statutory requirement to notify them.

Tuberculous meningitis remains a serious disease, and indeed two of the 20 children were known to have died; in one the diagnosis was made at necropsy and the other died shortly after diagnosis. An important finding was that 15 of the children (including nine white and five of Indian subcontinent ethnic origin) were aged less than 5 years (six of them less than 2 years) and were thus in the age group that could be protected by BCG vaccination at birth. Only two children (one from each group), however, were known to have had BCG vaccination. Although the evidence is limited, there seems to be a substantial level of protection.¹⁷ The diagnosis was confirmed on smear examination of the cerebrospinal fluid in only seven of the children, so this rapid confirmation of the diagnosis was obtained in only a third of the cases. It is often necessary to start treatment in the absence of positive bacteriological confirmation of the diagnosis as the importance of the early initiation of treatment in preventing both death and permanent neurological sequelae is well known. A rapid diagnostic test would be of major importance, particularly for patients whose cerebrospinal fluid is negative on smear examination. Such a test, based on the detection of mycobacterial antigen in the cerebrospinal fluid by latex particle agglutination has recently been reported by Krambovitis and colleagues.¹⁸ Although based on a relatively small number of patients, there seem to be

encouraging prospects for a simple and rapid test. Other groups are also investigating methods of detection of mycobacterial antigen and antibody in the cerebrospinal fluid.¹⁹

The continuing decline in the incidence of tuberculosis, both in the white and in the Indian subcontinent ethnic groups, is a reassuring finding but the high rates even in the young children of Indian subcontinent ethnic origin born in the United Kingdom indicate the higher risk of infection to which they are still exposed. It is therefore important that adequate measures for detection and treatment of the disease and for prevention by BCG at birth are maintained, especially in the areas with large immigrant populations.¹¹ Close cooperation between chest physicians and paediatricians is particularly necessary as many of the cases in children, 45% in the present survey, were diagnosed through contact tracing.

Despite the continuing decline in notification rates at all ages in the white population, small outbreaks of tuberculosis arising from a highly infectious source case and often affecting children, are still occurring.^{20 21} One recent outbreak occurred in a paediatric ward where many exposed children were immunosuppressed.²² Other outbreaks have occurred because of cases of the disease in the medical and nursing staff who were working on paediatric and obstetric wards; this emphasises the need to adhere to current occupational health guidelines.^{9 11}

The success of this survey was due to the enthusiastic cooperation of all (over 200) the medical officers for environmental health in England and Wales, all (nearly 400) the chest physicians and general physicians with a special interest in chest disease, over 400 clinicians in other specialties who provided information and chest radiographs; and to nursing staff, secretaries, and records officers of many hospitals and chest clinics, and to the infectious diseases clerks and other local authority staff.

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This survey was planned, coordinated, analysed, and written up by Dr MJ Humphries, coordinator, Mr AJ Nunn, statistician, Mr SP Byfield, programmer, Dr JH Darbyshire, and Professor Fox of the Medical Research Council Tuberculosis and Chest Diseases Unit and Dr KM Citron, consultant physician, Brompton Hospital. Radiological assessments were made by Dr M Caplin. The contribution of the Communicable Disease Surveillance Centre (Dr NS Galbraith) and the Mycobacterium Reference Unit (Dr PA Jenkins) of the Public Health Laboratory Service was coordinated by Dr ON Gill.

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Protective effect of BCG vaccination in infant Asians: a case-control study

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SUMMARY BCG vaccination has been routinely offered to infant Asian children in Birmingham since 1965. We conducted a case-control study to assess the protective effect of this scheme. Altogether 108 Asian children aged under 13 years, born since 1965, received treatment for tuberculosis. For each case four controls were selected; they were matched to the case by month and year of birth, sex, and ethnic origin. Cases and controls were all born in Birmingham. Of the cases, 62 out of 108 (57%) had received BCG, and of the controls, 336 out of 432 (78%) had received BCG. The estimated protective efficacy of vaccination was 64% (95% confidence limits, 43% and 77%).

Routine BCG vaccination in infant Asians confers useful protection against the development of tuberculosis in childhood.

The school BCG vaccination scheme in England and Wales continues to provide a high degree of protection against the development of tuberculosis in adolescents and young adults.¹ The annual notification rate for tuberculosis in the white indigenous population, however, has now fallen to 6.9/100 000² and it has therefore been recommended that the scheme be discontinued before 1990 provided that the downward trend in notifications continues.³ Children born in the United Kingdom of Asian immigrant parents have a notification rate at least 20 times as high as that in white children,⁴ hence it has also been recommended that newborn Asians and other groups at high risk of developing tuberculosis should continue to receive BCG.³ In 1986, 113 health districts in England and Wales routinely offered BCG to newborn Asians (CL Miller, personal communication), but little is known about the effectiveness of these vaccination schemes.

We therefore conducted a study on the effectiveness of BCG vaccination in infant Asians in Birmingham using the case-control method.⁵

Patients and methods

BCG SCHEME IN BIRMINGHAM

BCG vaccination has been offered routinely to all Asian infant children born in Birmingham since September 1965. This was given to children three

months after birth at a central clinic by a doctor and team of health visitors experienced in vaccination technique. Freeze dried vaccine (0.1 ml, Glaxo Laboratories Ltd; 8–26 colony forming units/ampoule) was injected intradermally over the insertion of the left deltoid muscle using a syringe and needle. In all cases tuberculin testing was performed three days before vaccination. Tuberculin testing was repeated three months after vaccination, except in 1969–70. This was usually performed by Mantoux testing using 10 units of tuberculin purified protein derivative. The result was read after three days and induration of 5 mm or more when read across the forearm was regarded as a positive result.

From 1979 onwards most vaccinations were given immediately after birth at Birmingham maternity hospitals in order to increase the coverage of the vaccination scheme. The present study was confined to subjects born between 1965 and 1979 who were eligible for BCG vaccination three months after birth under the original scheme and who developed tuberculosis before the age of 13 years.

Asian children reaching the age 13 years are again routinely tuberculin tested under the school BCG scheme and offered vaccination if tuberculin negative.

In 1966, 1440 children were born in Birmingham to parents of Asian or mixed Asian origin. By 1978 this had increased to 2842; the average annual number of births over this period was 2304.⁶

SELECTION OF CASES

Cases of tuberculosis in Birmingham were ascertained from the notification register. Details of each patient's place of birth and ethnic origin are included in the notification records. Information was obtained on all Asian children notified up to the end of 1935 who were born in Birmingham after the inception of the BCG scheme. Further clinical details on all patients were obtained by examining the casenotes and radiographs. Where casenotes were unobtainable, details were obtained from the general practice records.

A diagnosis of tuberculosis was accepted if there was bacteriological or histological evidence of tuberculosis, or if there was pulmonary disease without positive bacteriology, or if there were radiological features consistent with tuberculosis that resolved after antituberculous treatment. Lymph node disease was diagnosed on the basis of histology, and in some cases, on the basis of clinical examination if there was persisting lymphadenopathy and a history of close contact with a case of tuberculosis. In all other cases of non-pulmonary disease, a diagnosis of tuberculosis was only accepted if there was a positive bacteriology or histology result.

Notified subjects given antituberculous treatment, whether tuberculin positive or negative, who had no clinical, radiological, or bacteriological evidence of tuberculous disease were considered to have received chemoprophylaxis and were excluded from analysis.

Patients' vaccination histories were obtained from the vaccination records, which are kept in a central filing store. Patients who had received BCG vaccination at birth or at any other time because of known contact with a case of tuberculosis were excluded from the study. Likewise, children notified after the age of 12 years were excluded because of their eligibility for inclusion in the school BCG scheme.

SELECTION OF CONTROLS

Controls were selected by examination of the vaccination records. They were all subjects born in Birmingham, and they were matched to cases on the basis of month and year of birth, sex and Asian ethnic origin—only subjects with recognised Asian names were chosen.⁷

The vaccination records are filed according to month and year of birth. The records for individuals born in a particular month are filed in consecutive drawers. Within these drawers, for a given month, records are filed in alphabetical order. Controls were chosen by randomly selecting one of the drawers containing the records corresponding to the month and year of birth of a given case. Within a

selected drawer the first four records that fulfilled the matching criteria were examined, this meant that for each case information on four individually matched controls was obtained.

Subjects who had received BCG at any time other than under the scheme for newborn Asians were excluded.

STATISTICAL ANALYSIS

The relative risk of contracting tuberculosis in the vaccinated group compared with the risk in the unvaccinated group was estimated by calculation of the odds ratio (ψ)⁸ and appropriate confidence limits.⁹ The 'protective efficacy' of vaccination and the percentage reduction in cases of tuberculosis in the BCG vaccinated group compared with the unvaccinated group is given by $(1-\psi) \times 100$.⁵

The proportion of potential new cases of tuberculosis in Asian children prevented, the 'prevented fraction',¹⁰ is given by $\rho(1-\psi)/\rho(1-\psi)+\psi$, where ρ is the proportion of cases given BCG.

Calculations were performed using published programmes.¹¹

Results

The total number of tuberculosis notifications up to the end of 1985, for Asians born in Birmingham between September 1965 and December 1978, was 267. Most patients were followed up at the Birmingham Chest Clinic; the others were treated at four other hospitals within Birmingham. From this total, 159 (60%) subjects were excluded from the analysis for the following reasons: 113 (42%) were given chemoprophylaxis only, 25 (9%) were older than 12 years, 14 (5%) were given BCG because of contact with a case of tuberculosis, and one patient died at two months of disseminated tuberculosis discovered on postmortem examination before being eligible to receive vaccination. Six subjects (2%) were excluded from analysis because either clinical details or information on vaccination states were not available.

Of the 108 cases included in the final analysis, 47 (44%) were boys and 61 (56%) girls; 59 (55%) were of Indian ethnic origin, and 49 (45%) were of Pakistani or Bangladeshi origin. Respiratory disease only was present in 79 (73%), non-respiratory disease only in 22 (20%), and both respiratory and non-respiratory in seven (7%). Altogether 21 samples gave a positive culture, mainly from gastric washings; seven of these samples were smear positive. Sites of disease are given in table 1.

The principle findings are shown in table 2. Of the cases the reason that the vaccination had not been given was unrecorded in 31 children, 15 others

defaulted. In the controls, the reason that BCG had not been given was unrecorded in 73 children; 22 others defaulted, and one refused.

For analysis the results were expressed in terms of the vaccination state of each matched set of four controls (table 3). The estimated protective efficacy for the vaccine was 64% with 95% confidence limits of 43% and 77%. The prevented fraction was 0.50—that is, BCG prevented 50 out of every 100 potential new cases of tuberculosis.

In all cases and controls tuberculin testing before vaccination gave a negative result. Thirty six cases had postvaccination tuberculin testing performed.

In 31 (86%) the result was positive; three were positive when retested and two were revaccinated. The mean (SD) diameter of the Mantoux reactions in those cases vaccinated was 8.7 (2.1) mm. Post-vaccination tuberculin testing was done in 193 controls. In 184 (95%) the result was positive; seven others were positive when retested, and two defaulted. The mean (SD) diameter of postvaccination tuberculin reactions in the controls was 9.4 (2.7) mm. This was not significantly different from the mean postvaccination reactions in the cases who had been vaccinated (normal deviate test).

Discussion

There are little data on the effectiveness of BCG vaccination in the newborn in the United Kingdom. In Manchester, 10 326 neonates were vaccinated at a group of maternity hospitals between 1951–60; 15 152 babies born at the same hospitals did not receive vaccination. Over the same period 42 children born in the same hospitals developed tuberculosis: all of these cases came from the unvaccinated group.¹² A follow up study in children born between 1965–80 showed that BCG gave a protective effect of over 75%.¹³

Similarly, there are little data from studies based in the United Kingdom on the value of BCG vaccination in Asian subjects. Evidence that BCG vaccination protects against tuberculosis in Asian subjects comes from a contact study¹⁴: seven out of 425 (2%) contacts of patients with tuberculosis who were vaccinated developed tuberculosis compared with 57 out of 1479 (4%) unvaccinated contacts.

Recent studies on the efficacy of BCG in the newborn, mainly sponsored by the World Health Organisation, gave results similar to ours and showed a protective efficacy of between 53% and 74%.^{15–18} These agreed with earlier studies on BCG vaccination in the newborn, which consistently showed a beneficial effect,^{19–20} but are in marked contrast to the widely divergent results of prospective BCG trials in adolescents and young adults in several countries, some of which showed negative results.^{21–22}

Case-control methods to evaluate the effectiveness of BCG vaccination are quicker and less costly than are prospective methods, but they are more susceptible to bias.⁵ Control subjects in the present study were not clinically examined, therefore the presence of tuberculosis in some of these subjects cannot be excluded. Most cases of tuberculosis in childhood, however, arise as a result of close contact with an infected adult, and under the contact tracing system in Birmingham children in contact with known adult cases will have been examined.

Table 1 Site of disease (No of cases=108)

Respiratory disease (radiographic assessment)	
Enlarged nodes only	34
Pulmonary lesion with enlarged nodes	22
Pulmonary lesion only	17
Pulmonary and pleural	3
Pleural only	1
Normal (positive gastric washings)	2
Non-respiratory	
Lymph nodes	9
Miliary	5
Bone and joint	3
Peritoneal	2
Bowel and urinary tract	1
Meninges	1
Conjunctival	1
Respiratory and non-respiratory (site of non-respiratory disease given)	
Lymph nodes	5
Ileocaecal	1
Dactylitis	1

Table 2 No (%) of cases and controls given BCG vaccination

	Cases	Controls
No given BCG (%)	62 (57)	336 (78)
No not given BCG (%)	46 (43)	96 (22)
Total	108	432

Table 3 Sets of four controls classified according to number vaccinated and to vaccination state of matched case

	<i>No of controls (per set of four) given BCG</i>					
	<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>Total</i>
Sets matched to vaccinated cases	0	0	12	23	27	62
Sets matched to unvaccinated cases	0	3	12	16	15	46

Although all the control subjects were of Asian origin, they were not individually matched according to whether the matched case was of Pakistani or Bangladeshi or of Indian origin. Additionally, they were not individually matched according to socio-economic state as this information was not available from the vaccination records. A wide disparity in the proportion of cases and controls coming from different ethnic and social backgrounds could have biased the results if the coverage of the scheme differed in any important respect between ethnic and social groups within the Asian community. It was noted that cases and controls, however, came from similar districts within Birmingham, and these tend to be ethnically and socially homogeneous. The method of selection of controls should have prevented a preponderance of subjects from any particular social or ethnic grouping.

A study carried out in Birmingham, when neonatal BCG vaccination of newborn Asians was first introduced into Birmingham maternity hospitals in 1979, showed that only 69 (46%) out of 149 children were Mantoux positive after 22 months.²³ The authors suggested that this result could be explained by reduced cell mediated immunity in neonates. A similar study from Bradford showed that 59 (45%) out of 131 Asian babies given BCG within the first three months of birth gave negative or grade 1 Heaf reactions when tested between the ages of 3 months and 2 years.²⁴ Conflicting results from another centre in the United Kingdom showed that 353 (98%) out of 361 Asian neonates given BCG were tuberculin positive when tested three months later²⁵; these results accord with those of the present study. If impaired immunity was the cause of diminished tuberculin sensitivity after vaccination then a fairly constant proportion of Asian children would be expected to be non-responders to tuberculin after vaccination. A more likely explanation for the foregoing results is variation in the quality of vaccine administration both within and between different centres in the United Kingdom.

In the 1973-9 national survey of tuberculosis in England and Wales, 23% of the notified cases of childhood tuberculosis were receiving chemoprophylaxis¹ compared with 42% in the present study. There are two possible explanations for our higher figure. Firstly, physicians in Birmingham may have more readily notified children receiving chemoprophylaxis than physicians elsewhere. Secondly, because we had access to patients' case notes and full sets of radiographs, it is possible that we were better able to distinguish cases of tuberculosis from children given chemoprophylaxis; in the 1978-9 national survey, assessment was based only on a single pretreatment chest radiograph

and on information provided by the notifying physician.

Most of the children given chemoprophylaxis were treated solely on the basis of a positive tuberculin test, which may have been induced by previous BCG vaccination. Inclusion of these subjects in our analysis would have resulted in a reduction in the observed effect of the vaccine.

This study has shown that routine BCG vaccination in infant Asians in Birmingham confers useful protection against the subsequent development of tuberculosis in childhood. Further studies are required to assess the overall value of routinely vaccinating Asian newborn children, taking into account not only the efficacy of the vaccine, but also the declining incidence of tuberculosis in the Asian community in the United Kingdom,² the cost of treatment for tuberculosis, and the loss of tuberculin testing as a diagnostic tool once BCG has been given.

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Monitoring for central apnoea in infancy—limitations of single channel recordings

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SUMMARY Apparent central apnoea (absent breathing movements) detected by monitoring movement of the thoracic wall was compared with simultaneous detection by abdominal wall movement. Eighteen infants provided one or more 24 hour recording of heart rate (electrocardiography), thoracic respiration (transthoracic impedance), and abdominal wall movement (pressure sensitive capsule distortion). Detection of true apnoea, recognition of artefact, and measurement of the duration of true apnoea were all improved when two channels of respiratory monitoring were used in combination. We recommend that any study purporting to observe breathing patterns by indirect recording of respiratory movement will be more reliable if more than one channel of respiratory movements is recorded simultaneously. Further, in infants no estimation of duration of central apnoea can be made on the basis of either a transthoracic impedance record alone or an abdominal wall movement sensor alone. Comparison of findings among studies using different single channel recordings are unlikely to be meaningful.

Several reports on the occurrence of central apnoea in infancy have been based on information provided by a single respiratory channel that detects cessation of either chest or abdominal movements.¹⁻⁶ The work of Henderson-Smith and Read⁷ Curzi-Dascalova,⁸ and our own observations of polygraphic recordings, however, led us to question the reliability of this approach as the relative contributions of chest and abdominal movements to respiratory excursion may vary considerably among infants and, over a short time period, in the same infant. As a preliminary to studying patterns of central apnoea and heart rate in infants in the home, we recorded simultaneously chest and abdominal movements on independent channels and compared information obtained regarding central apnoea for each channel with that derived from the two channels combined. We made no attempt to detect obstructive apnoea—cessation of airflow at the mouth and nostrils with continuing respiratory movements²—as the use of airflow sensors is impracticable in the home setting. Our recording system also included heart rate. We present evidence that the recording of both chest and abdominal movements simultaneously improves the detection and quantitation of central apnoea.

Subjects and methods

The subjects, 11 boys and seven girls, were a subgroup from 50 infants being studied prospectively for respiratory pauses and heart rate during sleep at different ages through infancy. Five had been born prematurely but had recovered from all neonatal problems by the time of discharge home. Each was clinically normal and apparently healthy. The infants had at least two 24 hour recordings in the home between 46 and 60 weeks postconception.

Simultaneous recordings of the electrocardiographic and respiratory signals from the thorax were obtained using a single pair of paediatric adhesive electrocardiographic electrodes applied on opposite sides of the chest on the anterior axillary lines at the level of the nipples. The initial adequacy of the respiration signal was confirmed by the doctor who prepared the infant for recording either by checking a visual oscilloscope signal during quiet breathing or including a calibration period at the start of the tape for later inspection. The electrocardiographic and transthoracic impedance signals from these electrodes were recorded on a Healthdyne infant monitor incorporating a Medilog I 24 hour four channel ambulatory taperecorder. The abdominal

movement signal was obtained using a Graseby MR10 respiration monitor. This device has as its sensor for respiration a soft plastic capsule taped firmly to the anterior abdominal wall. Air pressure variations within the capsule associated with abdominal wall movement are transmitted along a fine plastic tube to the monitor.⁹ This instrument was modified to provide a continuous analogue electrical signal representing the pressure waves within the capsule that was recorded on a third channel of the tape recorder in the Healthdyne monitor in addition to the electrocardiographic and thoracic impedance signals. The alarm facilities of the monitors were not used in the present study.

A specially trained senior physiological measurement technician (GB) continuously monitored the signals on a large screen oscilloscope during the playback. The tapes were replayed at a speed 60 times faster than the original recording speed and the electrocardiographic and the two respiratory signals fed to solid state electronic buffer memories that allowed signals to be captured at any time during analysis. The two respiratory signals were also fed to a purpose built apnoea analyser that compared the amplitude of each respiratory waveform with a threshold that had been adjusted by the operator to 25% of the amplitude of the respiratory signal during a calibration period in which the infant was at rest and breathing quietly. This 25% rule was more stringent than either an arbitrary visual threshold or both monitors' own breath detection threshold. Movements with amplitudes less than a quarter of this were considered not to be associated with appreciable ventilation and could be discounted as effective breaths.

The analyser could be switched to measure the time between successive breath detections in (a) the thoracic impedance channel alone, (b) the abdomi-

nal pressure channel alone, or (c) the two channels taken together. In this last mode the duration of an apnoeic pause was thus the period during which neither the thoracic nor abdominal channel detected a breath.

An adjustable 'apnoea duration threshold' was provided in the analyser; this could be set to generate an output automatically whenever the breath-to-breath interval as defined by one of the above detection modes exceeded a chosen value. An electronic progress clock within the analyser accumulated the total time during which analysis was in progress.

Each time an episode of apnoea was detected the analyser output was used to 'freeze' the whole system: this stopped the tape replay and the progress clock and captured in the buffer memories the last 40 seconds of the electrocardiographic and respiratory waveforms. The signals could then be further examined on the oscilloscope screen and both respiratory traces printed out with the corresponding electrocardiographic signal (fig 1).

The operator was provided with a hand held push button control box from which the system could be 'frozen' manually for detailed inspection of disturbances noticed on the monitor screen. Another push button on the control box was used to disable analysis and stop the progress clock while allowing the tape replay to continue past any periods in which the quality of the recorded signals was inadequate because of recording artefacts. At the end of the tape the progress clock was read to obtain the total record duration actually analysed for that patient.

We elected to analyse 100 pauses >10 seconds for each respiratory channel (chest and abdomen). To ensure that a wide range of different recordings was included we selected by random numbers 27 tapes for scrutiny. As a single tape with frequent apnoeic

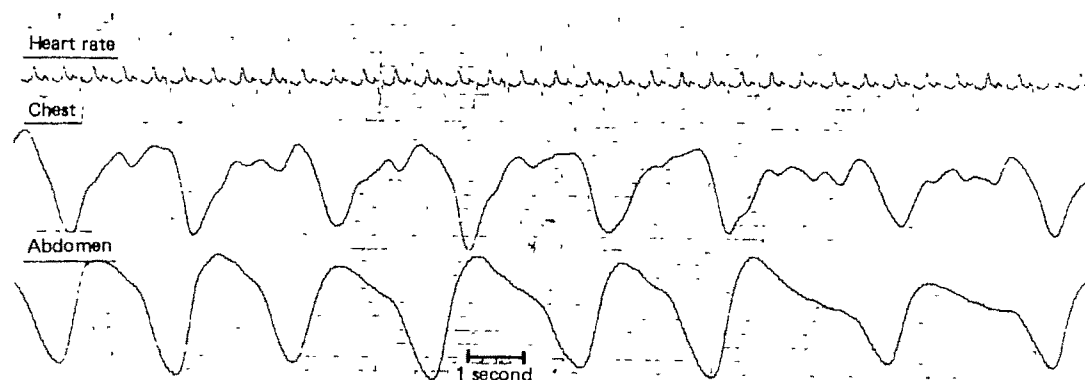


Fig 1 Corresponding heart rate, transthoracic impedance, and abdominal movement during normal quiet breathing.

pauses could easily have resulted in 100 pauses from the same recording, we used a sequential sampling technique whereby the first three pauses of each tape were studied and analysis continued using the next tape in the series. Once all 27 tapes had been sampled for the first three pauses >10 seconds the process was continued cycling through the parts of each tape not yet analysed. This resulted in all 27 tapes contributing to the documented results. The procedure was then repeated with judgments on the presence of central apnoea in each channel being made by visual inspection.

We defined bradycardia as a heart rate of <80 beats/minute for >10 seconds measured as sequential R-R intervals. We noted its occurrence in relation to central apnoea but made no attempt to quantify it in the tapes studied.

Results

The results were analysed using two criteria for absence of breaths on individual channels—one based on operator judgment and the other on the threshold for absent breaths as <25% of the amplitude seen in quiet breathing. There were no significant differences in the results obtained using these methods ($p>0.05$); findings for the former method are reported here. One hundred periods of absent chest signals (>10 seconds) were identified from a total of 559 hours of recording. The abdominal signal yielded 100 pauses from 266 hours of recording. The table gives the results obtained. On 30 occasions visual inspection suggested that transient poor lead contact was the cause of the sub-threshold signal (straight line appearance of apparent apnoea), while normal breathing movements were detected on the other channel. In the remaining 70 occasions where there were breathing pauses >10 seconds by transthoracic impedance, 33 (47%) were confirmed as true central apnoea of this duration after inspection of the second channel. In 13 (19%) instances breathing movements continued normally

on the second channel ('false' apnoea identified), while in a further 24 (34%) instances, the pause in respiratory movements in the abdominal channel was less than 10 seconds ('false' apnoea duration identified). Thus in 67 of 100 electronically detected episodes of apnoea and in 37 of 70 (53%) episodes of combined electronically detected and visually detected apnoea based on single channel transthoracic impedance data, the use of a second respiratory channel altered the interpretation in qualitative or quantitative terms.

When the abdominal respiratory movement channel was inspected a similar discrepancy was seen between single channel and dual channel findings. The number of signal failures interpreted as apnoea was much smaller, only 2%, but in 59 instances (60%) the abdominal channel was silent for 10 seconds or more while the thoracic channel continued to show normal breathing movement. On 15 (15%) occasions the duration of the pause in abdominal movement was up to 5 seconds longer than that in thoracic movement, altering the quantitative assessment of the apparent central apnoea. Figs 2-4 show patterns observed in simultaneous recordings of chest and abdominal movements.

Apparent apnoea on one respiratory channel and normal respiratory movements on the other was not associated with bradycardia. Like other investigators, however, we found that prolonged central apnoea was sometimes accompanied by bradycardia after a variable period of up to 15 seconds.¹⁰ Bradycardia occurring in association with apnoea may indicate arterial hypoxaemia, although this postulate has been challenged by Peabody *et al.*¹¹

Discussion

Both chest and abdominal movements contribute to the normal breathing movement patterns of infants with their relative contributions in individual infants changing with sleep state and body position.⁸ We have shown that this variation may also be relevant

Table Results of recording when <25% of the amplitude seen in quiet breathing was used as the respiratory threshold

Interpretation of both channels combined	100 pauses >10 seconds in thoracic movement	100 pauses >10 seconds in abdominal movement
Channels agree 'true' apnoea	33	10
Channels disagree	67	90
Normal breathing movement		
on other channels ('false' apnoea)	13	73
Duration of pause <10 seconds		
on other channel	24	15
Suspected signal failure		
(brief loss of background 'noise')	30	2

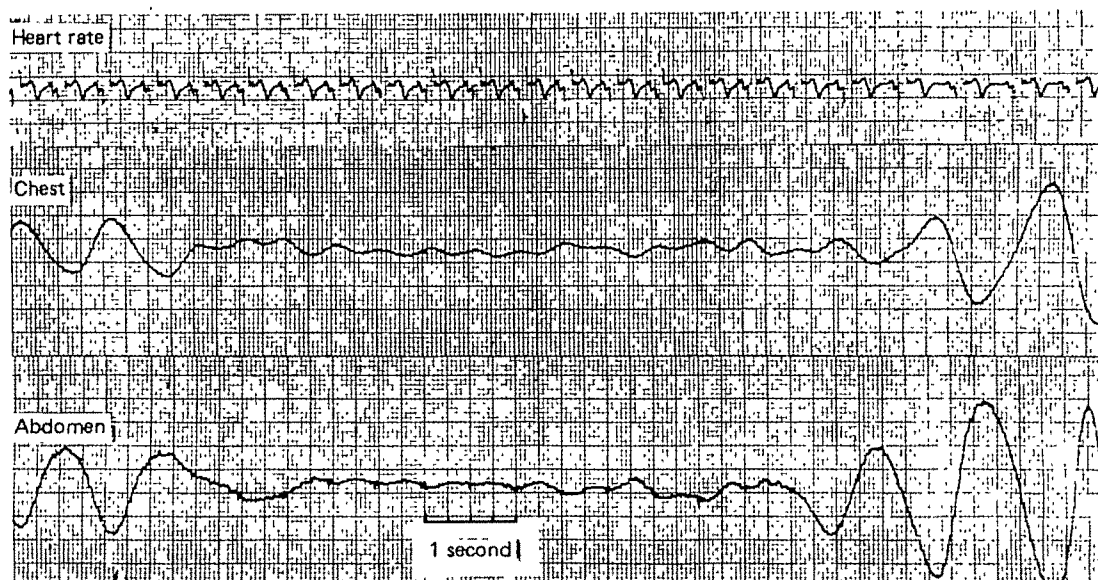


Fig 2 True central apnoea with absence of respiratory movement.

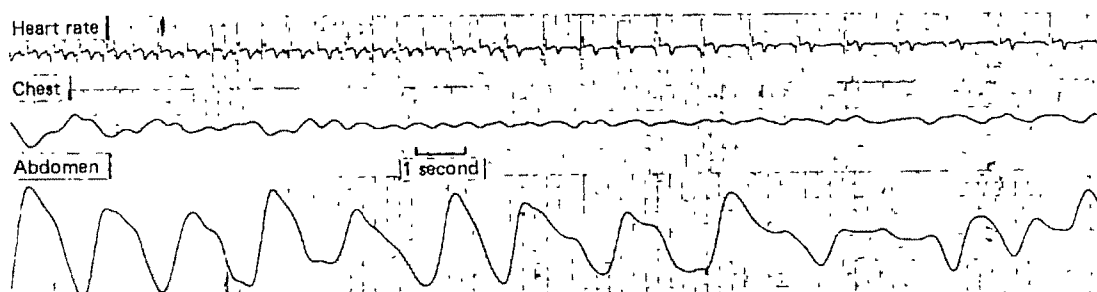


Fig 3 Absence of chest movement while abdominal movement continues—that is, adequate breathing appearing as apnoea when single channel only is observed

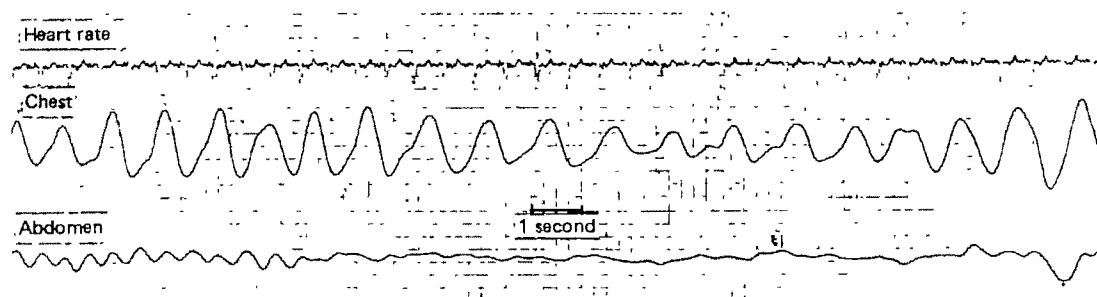


Fig 4 Absence of abdominal movement while chest movement continues

to the interpretation of central apnoea when a respiration monitor relies on only one component of respiratory movement. Transthoracic impedance changes as the chest circumference changes and gas content of the chest alters with breathing.¹² Although the theory of the method has been disputed,^{13,14} it is accepted as a useful measure of thoracic respiratory movement (or its absence) given appropriate lead siting and attachment. The brief signal failures detected in the present study, and which accounted for 30 discrepant results, commonly occurred during gross body movements when impedance signals could exceed maximum threshold. The remaining discrepancies between chest and abdominal signals were probably caused by the relative paucity of chest movements when breathing was predominantly abdominal.

Sensor or electrode detachment can contribute to observed errors using any method of monitoring. Faults in sensor attachment and signal production from the abdominal pressure capsule (for example, insecure taping to the skin) may be difficult to

identify. This highlights the need for a second method of respiration detection as a failsafe against over diagnosis of apnoea or of its duration. The initial studies describing the use of abdominal sensor capsule were performed in the neonatal period when spontaneous changes in body position (for example, rolling over) are less often seen than in older infants.² Variability of total abdominal wall excursion with each breath or in the site of greatest movement are evident when observing sleeping infants. Thus in studies that use the volume capsule to indicate cessation of respiratory movements any apparent absence of movement must be confirmed by an alternative method and the duration of pauses specified with reference to all breathing movements. Diagnosis or quantitation of central apnoea based on a single channel of respiration, using either of the monitoring systems described, is liable to lead to errors in the detection of apnoea, measurement of its duration, and analysis of prognostic risks.¹⁵

The possibility exists that our threshold for detection of apnoea was inappropriate. No pub-

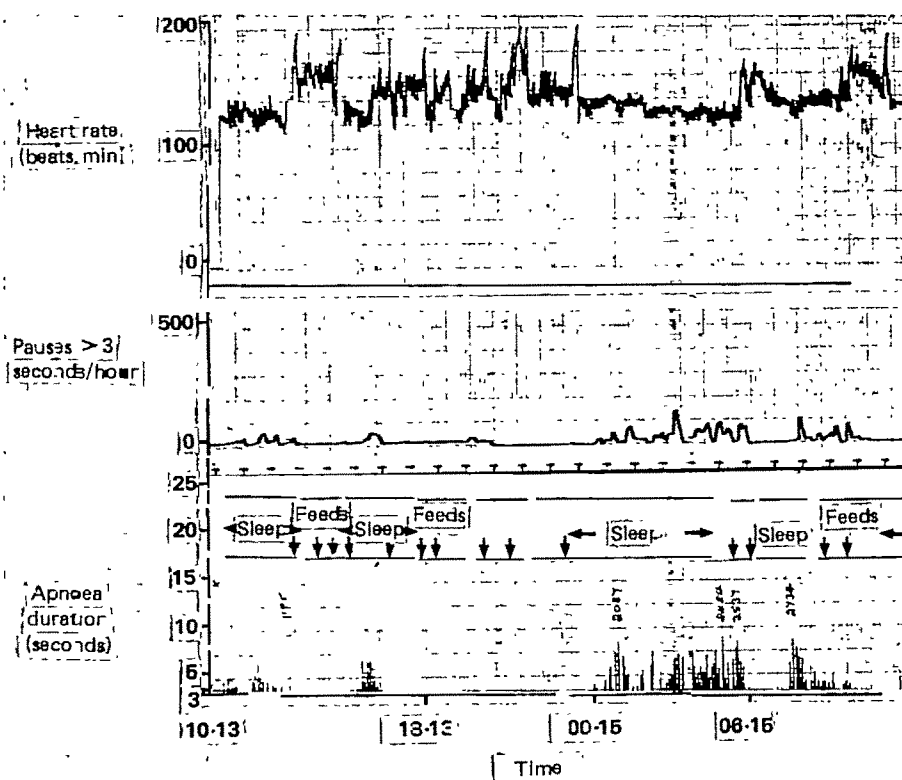


Fig 5 Typical 24 hour printout of heart rate, pauses >3 seconds/hour and apnoea >3 seconds frequency and duration in a normal infant. The apnoea duration trace represents each pause of 3 seconds or more as a vertical line whose height corresponds to length of apnoea as indicated on vertical axis

lished report on single channel recording of central apnoea gives precise guidance on detection criteria. We found that visual interpretation of cessation of movements on either channel resulted in as discrepant findings for chest and abdominal movements as the fixed threshold chosen. It is clearly impossible to be absolutely sure that apparent respiratory pauses on a single channel do indicate movement cessation with absent or ineffective breathing. The cessation of movement on both channels at the same time diminishes the likelihood of error.

Inclusion of heart rate is useful as an indication of adequate impedance electrode contact and in the detection of changes in heart rate, but it does not necessarily overcome the difficulty inherent in interpreting the results of a single channel recording. A normal heart rate allows no conclusions to be drawn about occurrence or duration of central apnoea. On the other hand, absence of respiratory movement on one channel with bradycardia is likely to confirm true central apnoea, though of uncertain duration. The occurrence of bradycardia may also relate to obstructive apnoea with continuing respiratory movements. Theoretically absence of movement on one channel, even when associated with bradycardia, does not preclude the occurrence of movements on the second respiratory channel although, in practice, this situation was not observed in the course of these recordings.

Our results indicate that interpretation of co-incident respiratory pauses of the duration observed (up to 20 seconds) by the methods outlined demands two channel respiratory monitoring. This does not infer that chest or abdominal movements are silent during periods of normal breathing but rather that breathing movement detection was imperfect using either of two commonly used monitoring systems. As a result of our findings on two channel monitoring we have studied patterns of respiratory pauses in infancy prospectively using two channels for respiration and one for heart rate (fig 5). This system detects the occurrence and duration of cessation of movements associated with respiration (central apnoea) and allows more precise interpretation of respiratory events associated with bradycardia than is possible with a single channel system.

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Inhaled bronchodilator treatment via the nebulhaler in young asthmatic patients

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SUMMARY Changes in functional residual capacity and peak flow rate were measured to assess bronchodilator response to terbutaline inhaled via a nebulhaler. In 10 children with asthma, aged 5–7 years, five breaths sufficient to operate the nebulhaler valve resulted in clinically important improvement in both the functional residual capacity and the peak flow rate. In 18 of 22 children, aged 2–5 years, who were too young to have their peak flow rate measured reliably, terbutaline administered via this modified nebulhaler technique was also associated with a clinically important change in functional residual capacity. The results suggest that effective bronchodilation using a nebulhaler can be achieved even in very young children.

Inhaled bronchodilator treatment has advantages compared with oral treatment: the onset of action is more rapid and smaller doses are required so there is less risk of side effects.¹ It is difficult, however, to give bronchodilator by inhalation to very young asthmatic patients other than by using a nebuliser. A pear shaped spacer device (nebulhaler) has been shown to be an effective means of administering bronchodilators to adults² and older children.³ Recently it has been suggested that it is not necessary to follow the manufacturers recommended manoeuvre of two deep inhalations from residual volume, but that five normal breaths of a sufficient magnitude to operate the nebulhaler valve resulted in effective administration of treatment.⁴ The latter manoeuvre is easy even for preschool children to perform.

It is difficult to assess bronchodilator response in young children who cannot reliably perform peak flow measurements. The measurement of functional residual capacity, however, is well tolerated and reproducible in children even as young as 2 years of age.⁵ Using this technique we have found that most young asthmatic patients have raised lung volumes⁶ and that nebulised bronchodilator treatment in such young children can be associated with a reduction in the functional residual capacity.⁷

In the present studies we first investigated changes in functional residual capacity and peak flow rate, after bronchodilator treatment via the nebulhaler, in children with asthma who were capable of performing both tests. Secondly, we investigated whether children with asthma who were

too young to have their peak flow rate measured reliably had a similar change in functional residual capacity on nebulhaler treatment.

Patients and methods

Ten consecutive children (nine boys, one girl; mean age 5.8 years, range 5.3–6.9) were enrolled into the first part of the study. Twenty two consecutive preschool children (14 boys, eight girls; mean age 3.6 years, range 2.5–4.9) were enrolled into the second part of the study. All the children were attending the paediatric clinic at King's College Hospital for the treatment of perennial asthma. Asthma was diagnosed after three separate episodes of wheezing and a clinical response to oral bronchodilator treatment. All children were receiving β adrenergic stimulants, and in addition 13 were being treated with theophylline orally and one of the older children inhaled steroids.

Permission for this study was granted by the King's College Hospital Ethics Committee. Informed parental consent was obtained.

All the children were studied in the paediatric respiratory laboratory at King's College Hospital; β adrenergic stimulants were omitted at least four hours before the measurement were taken.

On arrival the child's functional residual capacity was measured and when possible the peak flow rate. The child then received 500 μ g terbutaline via a metered dose aerosol through the nebulhaler. The canister was compressed to release a dose of 250 μ g. The child then took five breaths of sufficient

magnitude to move the nebulizer valve; this manoeuvre was then repeated. After 10 minutes measurements of functional residual capacity and peak flow rate (where possible) were repeated. As an assessment of symptomatic response, 10 minutes after bronchodilator treatment the child was asked if he or she felt less wheezy, the same, or worse. Children who failed to show either a clinically important change in either measurement (see below) were asked to reattend the laboratory at a later date for retesting.

RESPIRATORY FUNCTION MEASUREMENTS

Functional residual capacity was measured by helium gas dilution. The measurement was made with the child in a sitting position breathing through a water sealed spirometer (Gould Pulmonet 3) via a face mask. Equilibration was assumed when there had been a change of less than 20 ml in functional residual capacity over a 30 second period.⁶ In eight other young children with asthma (age 2–5 years) six measurements of functional residual capacity had been obtained; there was a mean coefficient of variation of 4%. Thus from these data and our previous results⁷ a clinically important change in functional residual capacity was designated as greater than 8% of predicted for height. Peak flow rate was measured by a Wright's Peak Flow minimeter and reported as the best of three separate measurements before and after bronchodilator treatment. Changes greater than 10% predicted for height were used as evidence of an important bronchodilator response.

All lung function measurements were performed by JBP and JG. Recordings of functional residual capacity were coded and subsequently analysed blind of clinical details by AG. Results of both measurements were expressed as a percentage of predicted for height using our own normal ranges for functional residual capacity⁵ and those of Murray and Cook for peak flow rate.⁸

STATISTICAL ANALYSIS

Bronchodilator response in both functional residual capacity and peak flow rate were assessed for significance using a paired Student's *t* test. The relation between changes in these measurements to the degree of hyperinflation before bronchodilator treatment was assessed for significance using Spearman's correlation.

Results

All but one child admitted to feeling better after the administration of terbutaline by the modified nebulizer technique. In all 10 older children there was a

significant change in both measurements: an increase in peak flow rate and a decrease in functional residual capacity ($p < 0.01$) (fig 1). The response, however, was variable, with a mean change in peak flow rate of 38.5% (range 10–65%) and mean change in functional residual capacity of 18.9% (range 8–44%). Sixteen of the 22 younger asthmatic patients showed a reduction in functional residual capacity after bronchodilator treatment, ($p < 0.01$) (fig 2). In all children the change in peak flow rate and functional residual capacity correlated ($p < 0.01$) with the measurement of functional residual capacity before bronchodilator treatment ($r = -0.78$ peak flow rate, $r = 0.49$ functional residual capacity). Two young asthmatic patients showed an increase in functional residual capacity after bronchodilator treatment: 22% and 24% change, respectively. Both these children, though having frequent severe asthma attacks, had functional residual capacities

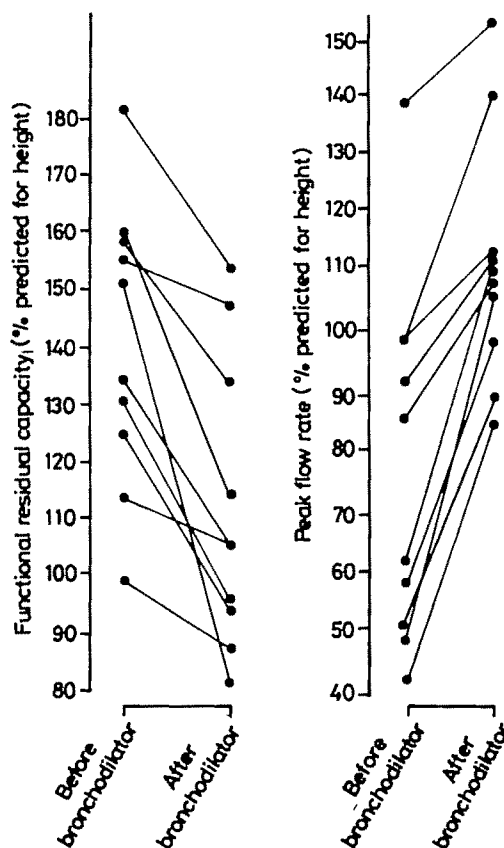


Fig 1 Functional residual capacity and peak flow rate before and after administration of bronchodilator via the nebulizer in the older children. Each child's results are shown by linked data points

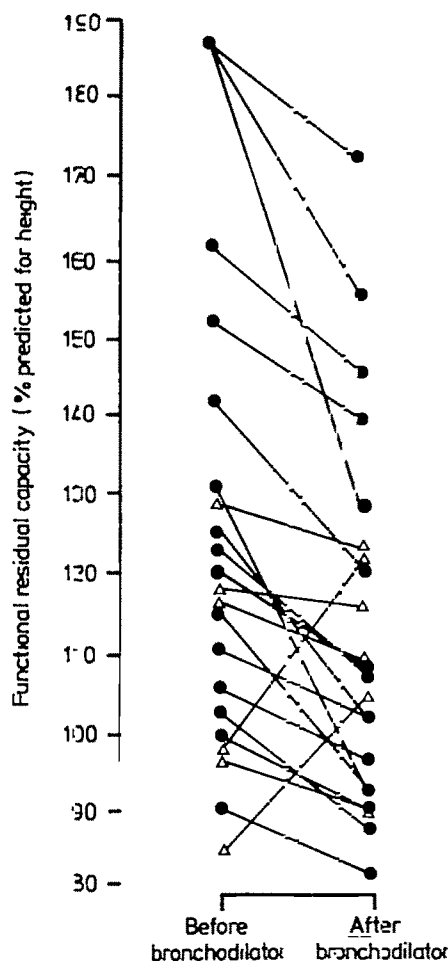


Fig 2 Functional residual capacity before and after administration of bronchodilator in the young children (2–5 years): each child's results are shown by linked data points. Children with a greater than 8% change in functional residual capacity after bronchodilator treatment (●), children with either a less than 8% change or an increase in functional residual capacity after bronchodilator treatment (Δ).

within the normal range before bronchodilator treatment: 101% and 83% of predicted for height, respectively.

Of the four young asthmatic patients who failed to show a clinically important change in functional residual capacity (>8%) after bronchodilator treatment, three have been recalled for at least two further measurements, and a variable response to treatment has been shown. In one child there was an increase in magnitude of change in functional residual capacity with repeat testing and in a second a greater than 8% change in functional residual

capacity occurred only when the child was coughing or wheezing, or both, at the time of measurement. The third child, despite being seen on a further three occasions, consistently failed to show a clinically important response to bronchodilator treatment. The fourth child, who showed neither symptom relief or a change in functional residual capacity after bronchodilator treatment, has not been recalled as he no longer attends the asthma clinic as he is symptom free at present.

Discussion

Bronchodilator treatment is more effectively administered by inhalation. Unfortunately young children have insufficient technical skill to coordinate the operation of a pressurised inhaler and inhalation, and as a consequence nebulisers have become increasingly popular. Nebulisers are large, require an outside power source, and are a relatively inefficient method of administration. Four to eight times the quantity of bronchodilator is necessary when given by a nebuliser to produce an equal effect,⁵ and at most 1% of the nebulised dose reaches the lung¹⁰ compared with almost 8% by a pressurised aerosol.¹¹ It has been shown that the attachment of a pear shaped spacer to the pressurised cannister increases the availability of the drug to the patient, even if inhalation is delayed by several seconds; this dispenses with the need to coordinate operation and inhalation.¹² This mode of delivery is more efficient in that the deposition of the drug in the lungs can be shown to increase to as much as 13%.¹¹

Recently a placebo controlled study has shown that the complicated instructions given by the manufacturers for correct nebuliser use are not necessary for effective administration of bronchodilator, making this method of treatment more widely applicable.⁴ A further study using a tube spacer rather than nebuliser showed that bronchodilation, assessed by changes in forced expiratory volume in one second, functional residual capacity, and residual volume, was similar if the child inhaled from residual volume or from functional residual capacity; bronchodilation was also similar whether the child inhaled as deeply as possible or only to about half the maximum volume.¹³ The present study confirms that in asthmatic children older than 5 years terbutaline given by modified nebuliser technique provides effective bronchodilator treatment. The changes in peak flow, confirming a bronchodilator response, were associated with changes in functional residual capacity. In a previous study changes in functional residual capacity were shown in response to salbutamol that was given

via a nebuliser and these changes were associated with symptom relief. Thus it was felt that the effectiveness of this treatment technique could be assessed reliably by measuring changes in functional residual capacity in children too young to perform peak flow measurements but in whom inhalation by nebuliser might confer numerous advantages.

In only 18 of the 22 young children tested was there a clinically important change in functional residual capacity. In two of these 18 children there was an increase in functional residual capacity after bronchodilator treatment. Both these children, though having frequent severe asthma attacks, had low functional residual capacities before bronchodilator treatment. A possible explanation for these results was that the children had such severe asthma that there was a limitation of gas mixing. The measurement technique showed that both children had a relatively low functional lung volume before bronchodilator treatment that increased after treatment and this was associated with symptom relief. Of the four children who showed no clinically important change in functional residual capacity, one was probably incorrectly included in this study as he no longer had asthmatic symptoms and thus would have been unlikely to respond to bronchodilator. Lack of a clinically important change in functional residual capacity in the other three children could be explained in two ways: firstly, an insensitivity of the measurement technique or secondly, failure of the treatment technique. It has been suggested that absolute functional residual capacity may not be a true guide to the amount of trapped gas and thus validity of measurements of functional residual capacity in determining hyperinflation could not be anticipated.¹⁴ We have, however, previously shown that functional residual capacity is raised in young asthmatic patients and that the degree of this rise is related to the severity of the asthma as judged by the amount of treatment required.⁶ We have also shown that in response to nebulised salbutamol during acute asthma attacks there is a reduction in functional residual capacity and a lessening of hyperinflation, which is associated with an appreciable improvement in compliance.⁷ Thus, plus evidence from the first part of our study that clinically important changes in functional residual capacity were always associated with a similar response in peak flow rate, suggests the measurement technique can reliably detect bronchodilator response. Thus the explanation for the three children in whom a clinically important change in functional residual capacity was not shown after bronchodilator treatment seems likely to be a failure

of method of treatment administration. This hypothesis is supported by the increase in magnitude of change in functional residual capacity after bronchodilator treatment that was shown in one child on repeat visits; this suggests a learning process.

From these results we would suggest that bronchodilator given by this modified nebuliser technique may be an effective form of treatment for young asthmatic children. We would also propose that a change in functional residual capacity may be used in young children, who are too young to perform peak flow rate, to confirm bronchodilator response.

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Natural cytotoxicity impairment in familial haemophagocytic lymphohistiocytosis

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SUMMARY Ten children with the characteristic clinical and haematological features of haemophagocytic lymphohistiocytosis are reported. Four patients treated with a combination of drugs comprising etoposide, methotrexate, and steroids were in complete remission after 10 to 30 months.

Natural cytotoxic mechanisms including natural killer cell activity, antibody dependent cell mediated cytotoxicity, lymphokine activated killer cell activity, and natural killer cell like activity were persistently absent or severely impaired in these four patients despite their clinical remission. Their parents and one healthy sibling also had impaired natural cytotoxic mechanisms. Constitutional impairment of natural cytotoxic mechanisms could be important in the pathogenesis of haemophagocytic lymphohistiocytosis.

Familial haemophagocytic reticulosis was first described by Farquhar and Claireaux in 1952.¹ Now known as familial haemophagocytic lymphohistiocytosis (FHL), it is a rare disease that is probably often wrongly diagnosed. It usually presents with fever, hepatosplenomegaly, and pancytopenia in infants.²⁻⁴ The central nervous system is often affected. Hypertriglyceridaemia and hypofibrinogenaemia are common, and often reversible with treatment.⁵ Genetic analysis of most of the sibships reported elsewhere indicates that there is an autosomal recessive inheritance in about 75% of cases.⁶ The disease has been rapidly fatal in most patients due to visceral infiltration of lymphocytes and histiocytes.² Initial attempts at treatment with plasma and blood exchange led to some improvement in the clinical course.⁷ Recently long term remission has been achieved by treatment with etoposide⁸⁻⁹ and teniposide.¹⁰ Combined treatment with etoposide, steroids, and methotrexate given intrathecally, seems to result in long term clinical remission, and preliminary results of prevention of fatal relapse from symptoms in the central nervous system by cranial irradiation have been reported.¹¹

Evaluation of the immunological state of some patients has shown that in some cases impairment of the immune system is an essential feature of FHL.¹²⁻¹⁴ Impairment of natural killer cell activity has recently been reported.¹⁵

We report the clinical and immunological features of 10 new cases of FHL. In particular we investigated various natural cytotoxic mechanisms including natural killer cell activity, antibody dependent cellular cytotoxicity, lymphokine activated killer cell activity, and natural killer cell like activity generated in allogeneic mixed lymphocyte cultures in four affected children who achieved continuous complete remission, and in their families.

Patients and methods

Nine boys and one girl aged between 1 and 44 months from six Italian families were studied between 1983 and 1986. They all had FHL according to current diagnostic criteria.²⁻⁴ Cases 3 and 4 and cases 5 and 6 were brothers, and cases 1, 9, and 10 (the latter being male monozygous twins) were members of the same family. The families of cases 7 and 8, and of 1, 9, and 10, were also studied; they comprised six healthy parents aged from 25 to 35, and the 3 year old healthy brother of cases 1, 9, and 10. The control group (from whom the normal values were derived) comprised healthy adult subjects who underwent immunological evaluation at the same time as the patients.

CELL PREPARATION

Lymphocytes were isolated from heparinised peripheral blood as previously described.¹⁶

ASSAY OF NATURAL KILLER CELL ACTIVITY

The assay was performed as previously described.¹⁷ K562 cells were used as the target line, and they were labelled with 100 µCi of sodium ⁵¹chromate (New England Nuclear) for 60 minutes at 37°C. The cells were plated in duplicate in concentrations of 5×10³/µl, and varying numbers of effector cells were then added to give effector:target cell ratios of 100:1, 30:1, and 10:1. The plates were incubated in a humidified atmosphere containing 5% carbon dioxide for four hours at 37°C. After the incubation period the amount of radioactivity in the supernatant was measured by a gamma counter. The results were expressed as percentage cytotoxicity measured by specific release of ⁵¹chromate and calculated as follows: % release=experimental release minus spontaneous release/total release minus spontaneous release×100.

ASSAY OF ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY

P815 cells, which are resistant to the activity of natural killer cells, were sensitised with rabbit specific IgG before being used as target cells. These cells, in concentrations of 1–2×10⁶, were labelled with ⁵¹chromate and then incubated with antiP815 antiserum in a dilution of 1:10⁵ for 30 minutes at room temperature. The assay was performed under the same conditions as that of natural killer cell activity.

ASSAY OF LYMPHOKINE ACTIVATED KILLER CELL ACTIVITY

Lymphocytes were cultured in 24 well plates at a concentration of 2×10⁶/ml in 2 ml of Roswell Park Memorial Institute (RPMI) 1640 medium, which was supplemented with 10% human AB serum, 50 µg/ml gentamicin, and 2 mM glutamine (complete medium) in the presence of 500 U/ml human recombinant interleukin 2 (R IL-2, Roche). After being incubated for seven days in a humidified atmosphere with 5% carbon dioxide the cells were recovered and their cytotoxicity measured against Daudi target cells, which are resistant to the activity of natural killer cells, under the same conditions as described above.

ASSAY OF ALLOGENEIC MIXED LYMPHOCYTE RESPONSE AND NATURAL KILLER CELL LIKE ACTIVITY

Responder lymphocytes were cultured in 24 well plates at a concentration of 10⁶/ml in complete medium. Allogeneic human mononuclear cells were used as the stimulators after they had been irradiated with 2000 rads, and were added at the same concentration in a total volume of 2 ml. Cultures were incubated at 37°C in a humidified atmosphere with 5% carbon dioxide. After seven days cells were recovered and natural killer cell like cytotoxicity was measured against HL-60 target cells, which are resistant to natural killer cell activity, under the same conditions as described above.

Table 1 Clinical and laboratory data of 10 children with haemophagocytic lymphohistiocytosis

	Case nos									
	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	M	M	F	M	M	M
Familial occurrence	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Age at onset (months)	2	17	1	2	25	44	13	5	2	2
Fever (>38.5°C)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hepatosplenomegaly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lymphadenopathy	No	No	No	No	Yes	Yes	Yes	Yes	No	No
Jaundice	No	No	Yes	No	Yes	No	No	Yes	No	No
Skin rash	No	No	Yes	No	Yes	No	No	No	No	No
Polymorphonuclear leucocytes <1×10 ⁹ /l	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Platelet count <1000×10 ⁹ /l	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum fibrinogen concentration <1g/l	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum triglyceride concentration >1.7 mmol/l	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
White cell count in cerebrospinal fluid >5×10 ⁶ /l	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Erythrophagocytosis in bone marrow, and liver or spleen	Yes	Yes	Yes	Yes	*	Yes	Yes	Yes	Yes	Yes
Cranial radioprophylaxis (18 Gy in 10 doses)	No	No	No	No	No	No	Yes	Yes	No	No
Outcome	Died	Died	Died	Died	Died	Died	Well	Well	Well	Well
Age at death, or at time of writing (months)	4	23	12	20	26	46	43	24	12	12

*Observation not made by us

Results

These 10 children showed the clinical and laboratory features that are typical of FHL (table 1). Seven of the 10 had the familial disease, the other three being isolated cases.

Case 3 ran a fulminant course with a graft versus host reaction after a blood transfusion, so the diagnosis of congenital severe combined immune deficiency had to be excluded. Later his brother (case 4) developed typical FHL. The complete clinical record of case 5 was available from another hospital where the child had died of what had been assumed to be a lymphoproliferative disorder. Cases 1-6 all died of severe FHL, cases 5 and 6 within 26 months of age. The last four patients (cases 7-10) were still alive, and in continuous complete remission 10 to 30 months after diagnosis.

Immunological investigation of the 10 patients

showed an inconsistent pattern of abnormalities, as reported elsewhere.¹⁸ In the four surviving children (cases 7-10) natural killer cell activity, lymphokine activated killer cell activity, antibody dependent cellular cytotoxicity, and natural killer cell like activity were profoundly impaired despite continuous clinical remission; fibrinogen and triglyceride concentrations had returned to normal, and haemophagocytosis was no longer detectable (table 2).

Table 3 shows that the parents of the surviving patients and the healthy 3 year old brother of patients 1, 9, and 10 all showed impairment in their natural cytotoxic mechanisms. In particular natural killer cell activity was extremely low or absent in the mothers of cases 7 and 8, the father of 8, and in the healthy brother; it was at the lower limit of normal in the father of case 7. Antibody dependent cellular cytotoxicity was low in four of the six parents tested;

Table 2 Natural cytotoxicity evaluation in four surviving patients

	Effector target cell ratio	Surviving case nos				Normal values mean (SD)
		7	8	9	10	
Natural killer cell activity	100:1	2	6	34	17	61 (13)
	30:1	0	2	21	23	40 (12)
	10:1	0	0	10	17	28 (9)
Antibody dependent cellular cytotoxicity	100:1	0	28	7	10	68 (17)
	30:1	0	0	2	8	52 (15)
	10:1	0	0	2	2	27 (10)
Lymphokine activated killer cell activity	100:1	0	22	35	27	74 (14)
	30:1	0	15	26	9	53 (11)
	10:1	0	13	16	9	31 (9)
Natural killer cell like activity	100:1	0	2	22	12	55 (21)
	30:1	0	0	18	7	47 (13)
	10:1	0	0	7	4	22 (13)

Activities are expressed as % of specific lysis

Table 3 Cellular cytotoxicity and natural killer cell phenotype in six parents and one healthy brother of cases 7-10

	Effector- target cell ratio	Case 7		Case 8		Cases 1, 9, and 10			Normal values mean (SD)
		Father	Mother	Father	Mother	Father	Mother	Brother	
Natural killer cell activity	100:1	32	8	21	17	56	46	25	61 (13)
	30:1	18	4	15	8	46	45	28	40 (12)
	10:1	5	4	7	6	39	46	24	28 (9)
Antibody dependent cellular cytotoxicity	100:1	27	24	33	27	69	46	19	68 (17)
	30:1	21	12	30	18	76	33	12	52 (15)
	10:1	12	7	7	9	56	25	11	27 (10)
Lymphokine activated killer cell activity	100:1	52	52	19	10	16	71	54	74 (14)
	30:1	41	33	12	3	15	62	55	53 (11)
	10:1	23	21	4	2	7	59	46	31 (9)
Natural killer cell like activity	100:1	67	38	28	27	46	59	33	55 (21)
	30:1	64	26	15	22	19	48	21	47 (13)
	10:1	42	6	6	5	20	40	11	22 (13)
With monoclonal antibody Leu7		12	9	8	12	ND	ND	ND	18 (7)
With monoclonal antibody Leu11		18	7	15	14	ND	ND	ND	23 (6)

Activities are expressed as % of specific lysis. Leu7 and Leu11 are expressed as % of positive cells.

lymphokine activated killer cell activity was low in both parents of case 7 and in the father of cases 9 and 10, and natural killer cell like activity was low in the parents of case 8 and at the lower limit of normal in the mother of case 7 and in the brother of cases 1, 9, and 10.

Discussion

We have studied 10 cases of FHL from six Italian families. Three patients came from families with no other affected children, but were included as they showed all the clinical and laboratory features of FHL with the exception of a positive family history. It is reported that there is only a slight preponderance of males affected,⁶ whereas we found a male:female ratio of 9:1. The clinical course was severe and all but the last four children died, most within 2 years of age. The four surviving patients were treated with a combination of drugs (etoposide, steroids, and methotrexate given intrathecally). Cases 7 and 8 received cranial irradiation in a dose of 18 Gy, as recently suggested.¹¹ They were all in continuous remission at the time of writing after 10 to 30 months. How long chemotherapy should be continued in patients in remission is still debatable. We decided not to suspend treatment because of the severe prognosis and the evidence of early relapse after stopping treatment found by others (C Gris-cellì, personal communication).

The pathogenesis of FHL is unknown. A primary disorder of lymphocyte response with secondary impairment of the monocytic response has been suggested. A defect in natural killer cell activity that is reversible by cytotoxic treatment, has also been suggested.¹⁵ In the four surviving children in our report (cases 7–10), natural cytotoxic mechanisms including natural killer cell activity, antibody dependent cellular cytotoxicity, lymphokine activated killer cell activity and natural killer cell like activity were persistently absent or severely impaired even during the long lasting complete remission. Impairment of cytotoxicity is not due to treatment with drugs,¹⁵ because we detected it in the healthy, untreated subjects as well as the patients. Moreover, this study provides evidence that the parents and the only healthy brother of our patients with FHL have impairment of one or more of their natural cytotoxic mechanisms. These data suggest that the defect may be genetically transmitted from the healthy heterozygous parents to the offspring. In our patients impairment of natural cytotoxicity appeared to be a characteristic feature of FHL, independent of clinical state, typical biochemical aberrations, and treatment.

The present data are not in keeping with a

previous report of an apparently reversible defect in natural killer cell activity in FHL.¹¹ On the contrary, evidence of restoration of natural killer cell activity in a patient with FHL who received an HLA matched bone marrow transplant¹⁹ suggests that the successful graft led to clinical remission, and to biological replacement of the impaired lymphocyte clone. It can be hypothesised that in FHL functional imbalance of different natural killer cell subsets is responsible for the persistent severe impairment in natural cytotoxic mechanisms. Nevertheless, our results confirm previous reports^{20, 21} that showed that the percentage of circulating natural killer cells (calculated using Leu 7 and Leu 11 monoclonal antibodies) is low only in some patients, and does not correlate with low functional activity. Moreover, incubation with interferon (the production of which also seems to be impaired) has been reported as being ineffective in restoring natural killer cell activity in patients with FHL.²⁰

Natural killer cell activity develops in humans during the prenatal period, is still depressed in the newborn, and becomes complete—that is, the same as normal adult activity—within a few months.^{22–25} Nevertheless, newborn infants display normal or even high antibody dependent cellular cytotoxicity, natural killer cell like and lymphokine activated killer cell activities when compared with adult controls.²⁶

It was recently reported that homozygosity in the genes controlling the major histocompatibility complex influences natural killer cell activity in man.²⁷ Thus a link between the gene or genes controlling the development of FHL and those controlling the level of natural killer cell activity, which are all located close to the genes coding for human leucocyte antigen, could be possible. The various mechanisms of natural cytotoxicity are currently thought to play a principal part in the defence against proliferating aberrant cells or cells infected with viruses, as well as having a regulatory role in the modulation of hemopoiesis.^{28, 29} A persistent constitutional impairment of these mechanisms seems to be important in the pathogenesis of FHL. Moreover, the identification of this biological marker is also important as it may have a practical application if prenatal diagnosis is attempted.

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Family studies in ornithine transcarbamylase deficiency

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SUMMARY Six families with at least one infant each with confirmed ornithine transcarbamylase deficiency were investigated by DNA analysis. All the affected sons had died, and no DNA had been stored. Using the restriction endonucleases *Msp*I and *Bam* HI three restriction fragment length polymorphisms were detected which led to eight distinct haplotypes. Using these results and those of protein loading tests that diagnosed heterozygote (carrier) status in some family members, some carriers were detected, and prenatal diagnosis was offered to two families. In two further families no polymorphisms were found and no prenatal diagnosis was possible. In the remaining two families prenatal diagnosis was impossible because of the lack of DNA from an affected or unaffected son, or in one case from the father, of an obligate carrier.

These studies emphasise the importance of preserving tissue for DNA extraction from infants dying of inborn errors of metabolism, and also show the way in which information from conventional biochemical studies can complement diagnostic tests using DNA.

Deficiency of ornithine transcarbamylase (Enzyme Commission No 2.1.3.3), an enzyme in the urea cycle, is a severe X-linked disorder which results in hyperammonaemia and early death in affected hemizygote male infants.¹⁻³ Due to random inactivation of X chromosomes female carriers have variable amounts of enzyme activity and a less severe form of the deficiency. This may show itself in protein intolerance, cyclical vomiting, and mental retardation, although many carriers are asymptomatic.

Ornithine transcarbamylase is a mitochondrial enzyme expressed only in liver and small intestinal mucosa,¹ so prenatal diagnosis by chorionic villus sampling or amniocentesis is not possible. Detection of carriers has been attempted by giving an orotic acid free protein load and measuring urinary excretion of orotic acid and blood ammonia concentrations. Though a positive result can successfully indicate a carrier a negative result does not necessarily indicate normality because of the variability of enzyme activity that may approach normal in some carriers.¹ For example, an asymptomatic woman whose daughter and two infant sons died from ornithine transcarbamylase deficiency had normal protein loading tests.⁴

Isolation of the gene for ornithine transcarbamylase

has permitted an alternative approach to the diagnosis of the disorder by DNA analysis.⁵ Although the mutations responsible for the deficiency are unknown, in most circumstances the disorder can be detected by establishing linkage between the mutant gene and a restriction fragment length polymorphism within or near the gene locus.⁶⁻⁸ Once a restriction fragment length polymorphism has been closely linked to a particular gene, it may be possible to track that gene by its restriction fragment length polymorphism, which will be transmitted along Mendelian lines within a family. In this study we describe our experience using DNA linkage analysis for the detection of carriers and in prenatal diagnosis of six kindred at risk of ornithine transcarbamylase deficiency.

Patients and methods

Members of six kindred with ornithine transcarbamylase deficiency were studied. Figs 1a-f show the pedigrees of these families.

KINDRED A (fig 1a)

Ornithine transcarbamylase deficiency was diagnosed after the propositus (III 5) presented when 2 days old with hyperammonaemic coma and died

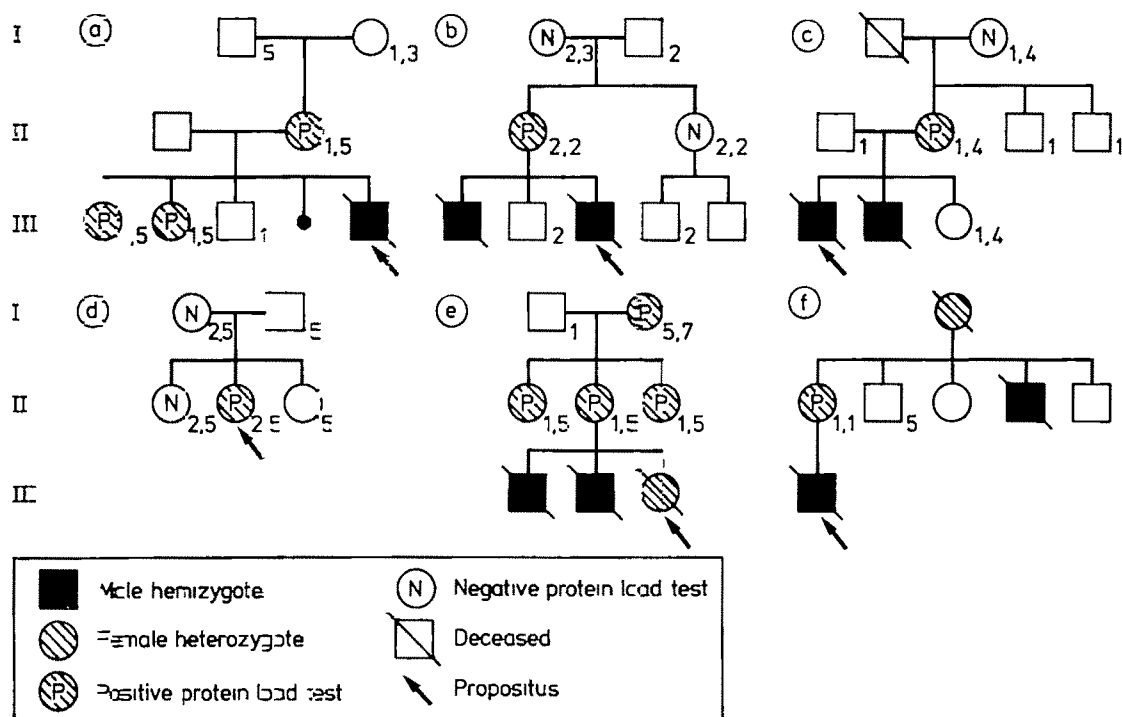


Fig 1a-f Pedigrees of kindreds A-F. Roman numerals indicate generations, Arabic numerals indicate haplotypes.

on day 4. Analysis of liver obtained by needle biopsy before death showed barely detectable ornithine transcarbamylase activity; other enzymes of the urea cycle were within the normal ranges. His mother (II 2) and two sisters (III 1 and III 2) had unequivocally positive results when given a formal protein loading test.⁹

KINDRED B (fig 1b)

The proband (III 3) died when 4 days old, having become hyperammonaemic on day 2. Ornithine transcarbamylase deficiency was suspected when analysis of the urine showed high concentrations of orotic acid, and plasma citrulline concentration was undetectable. The diagnosis was confirmed when ornithine transcarbamylase activity was found to be less than 10% of normal in liver obtained before death by needle biopsy. An earlier male sibling had died in identical circumstances, and the mother (II 1) was therefore diagnosed as an obligate heterozygote for ornithine transcarbamylase deficiency. Her protein loading tests were positive but those of her sister (II 2) and their mother (I 1) were negative.

KINDRED C (fig 1c)

The proband (III 1) died in the neonatal period and a diagnosis of ornithine transcarbamylase de-

ciency was suggested by analysis of blood and urine; this was confirmed by assay of liver enzyme activity. A second son (III 2) was treated for ornithine transcarbamylase deficiency from birth. This had been diagnosed by a low plasma citrulline concentration together with increased excretion of orotic acid in the urine. He was never hyperammonaemic and had remained well on treatment for eight months, when he died suddenly during an intercurrent infection. The mother (II 2) was thus an obligate heterozygote. Her mother (I 2) had a normal protein loading test.

KINDRED D (fig 1d)

The proband (II 2), a girl of 3 years old, was found to be a carrier for ornithine transcarbamylase deficiency after she presented with protein intolerance and cyclical vomiting. The diagnosis was suspected when raised concentrations of blood ammonia together with increased excretion of orotic acid in the urine were found. A liver biopsy specimen showed ornithine transcarbamylase concentrations of about 30% of normal. Neither her mother (I 1) nor her sister (II 1) showed any evidence of ornithine transcarbamylase deficiency and in both the protein loading tests were negative.

KINDRED E (fig 1c)

In this family the proband was a girl aged 18 months who presented with recurrent vomiting. She had increased excretion of orotic acid in the urine, a raised blood ammonia concentration, and raised plasma glutamine concentration, no other plasma amino acids were appreciably raised. She died of an ependymoblastoma at the age of 2½ years.¹⁰ Her mother (II 2) had had two sons both of whom died in the first week of life. Protein loading tests on the mother, her two sisters and their mother gave unequivocally positive results.

KINDRED F (fig 1f)

The mother (II 1) was diagnosed as a heterozygote for ornithine transcarbamylase deficiency on her family history and the positive results of a protein loading test. The proband, her son, died when 3 days old following the onset of vomiting and coma on day 2. Excretion of orotic acid in the urine was raised and the plasma citrulline concentration was undetectable. A sample of liver obtained by needle biopsy showed complete absence of cross reacting ornithine transcarbamylase protein. The mother's brother (II 4) had died aged 5 days of unknown cause.

DNA ANALYSIS

DNA was prepared by standard methods from the buffy coat fraction obtained from 10 ml of blood.¹¹ DNA (10 µg) was digested with restriction endonucleases *Msp*I, *Bam* HI, or *Taq* I (Pharmacia) under conditions recommended by the supplier. The resulting restriction fragments were separated by agarose gel electrophoresis (0.8% agarose, 16–18 hours at 1.8 V/cm) in Tris-acetate-EDTA buffer.¹² DNA transfer to nitrocellulose membranes, prehybridisation, and hybridisation were carried out by the methods described by Maniatis *et al.*,¹² with hybridisation in the presence of 50% formamide for 18 hours at 42°. The radioactive hybridisation probe was prepared by labelling a recombinant plasmid containing a full length of complementary DNA for human ornithine transcarbamylase⁵ to give a specific radioactivity of at least 10⁸ dpm/µg. After hybridisation the filters were washed for one hour at room temperature in 2× SSC (SSC=0.15M sodium chloride, 0.015M sodium citrate, pH=7.0), and then three times for 30 minutes each in 0.1×SSC at 65°. Bands were detected by auto-radiography at -70° using pre-flashed Fuji RX x ray film. Fragment sizes were measured by reference to *Hin* dIII-digested λ phage DNA.

PROTEIN LOADING TEST

After an overnight fast patients were given a protein

load of 1 g/kg body weight derived from steamed chicken breast. Fasting and 0 to six hours after the load urinary orotic acid concentrations were compared with those from age matched controls.⁵ Urinary orotic acid was measured by the method of Harris and Oberholzer.¹³

Results

The restriction endonuclease *Msp*I detected two separate restriction fragment length polymorphisms, the alleles measuring 6.6 and 6.2 kb pairs in one case and measuring 5.1 and 4.4 kb pairs in the other;

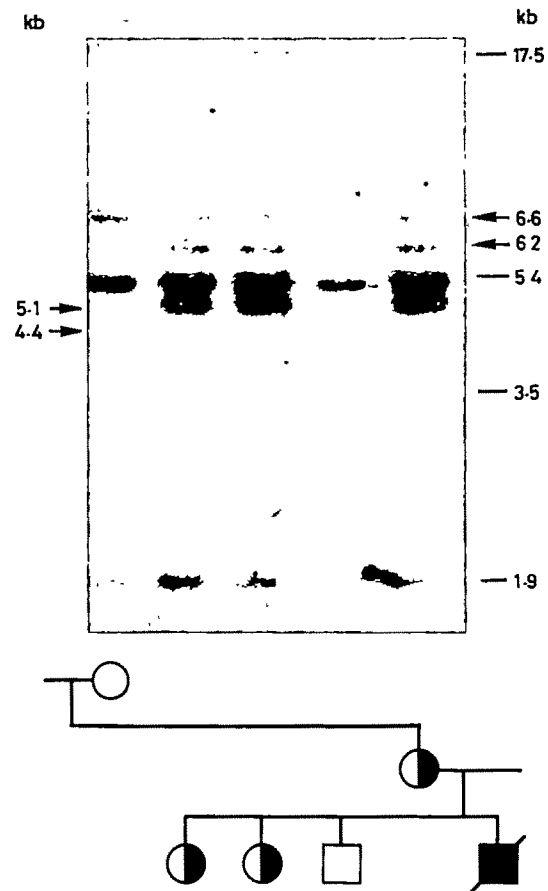


Fig 2 Partial pedigree and Southern blot analysis of family A with *Msp*I digested DNA hybridised with OTC cDNA. Band sizes are given in kb (kilobase pairs). Polymorphic sites are illustrated by arrows. The proband is shown as ■, carrier females as ●, normal female ○, normal male □. Each lane in the Southern blot is labelled with the pedigree designation of the family member whose DNA was analysed in that lane.

Bam HI gave a single restriction fragment length polymorphism comprising 1.8 and 5.2 kb bands (figs 2 and 3). As a result any X chromosome may have one of eight possible haplotypes—that is, combinations of the three pairs of alleles. The table shows haplotypes 1–8.

Haplotype construction was facilitated by analysis of restriction fragment length polymorphisms of an appropriate male subject from each family in whom the presence of a single X chromosome allowed the haplotype to be specified in all cases. Thus for females, it was always possible to deduce which restriction fragment length polymorphisms were linked to one another on the two separate X chromosomes.

KINDRED A

DNA analysis in this family was informative. The mother and her two daughters (II 1 and III 2) who were the presumed carriers had haplotypes 1,5. The unaffected son (III 3) had haplotype 1. The ornithine transcarbamylase mutant gene must therefore have been linked to haplotype 5. The maternal grandmother (I 2) had haplotype 1,3 and as she did not have the haplotype 5 that was linked to the mutant gene a spontaneous mutation must have

Table Assignment of haplotypes for restriction fragment length polymorphisms about the ornithine transcarbamylase gene

Haplotype	Restriction endonucleases	
	<i>Msp</i> I (kb)*	<i>Bam</i> HI (kb)
1	6.6 5.1	1.8
2	6.6 5.1	5.2
3	6.6 4.4	1.8
4	6.6 4.4	5.2
5	6.2 5.1	1.8
6	6.2 5.1	5.2
7	6.2 4.4	1.8
8	6.2 4.4	5.2

**Msp*I detected two restriction fragment length polymorphisms

occurred in either a germ cell from the maternal grandfather or in an early cleavage, and II 2 thus carried a new mutation. The maternal grandmother and her four sisters (not shown) could therefore be assured that they were not carriers.

KINDRED B

The proband's mother (II 1) was the only known carrier in this kindred. Her haplotype was 2,2 and as we detected no restriction fragment length polymorphism about the ornithine transcarbamylase gene, prenatal diagnosis could not be offered to her. Her mother (I 1) had haplotype 2,3 and her father (I 2) had haplotype 2. The maternal grandmother of the proband (I 1) and maternal aunt (II 2) had negative protein loading tests so that it was not certain whether this was a new mutation. If I 1 were a carrier, the maternal aunt with haplotype 2,2 would also be a carrier. II 2's affected X chromosome, however, could also have been derived from a new mutation in a germ cell from either her mother or her father, or from a mutation in an early cleavage.

KINDRED C

The mother of the proband (II 2) had haplotype 1,4, her mother had haplotype 1,4 and her two brothers II 3 and II 4 and her husband had haplotype 1. Her newly born daughter III 3 had haplotype 1,4. As the proband's maternal grandmother had a negative protein loading test it was uncertain whether she was a carrier. In this case prenatal diagnosis could have been offered to II 2 if DNA had been available from one of the affected sons (III 1 or III 2). Should the newborn daughter III 3 be confirmed to be a carrier by a loading test, however, then the defective gene would probably segregate with haplotype 4, because III 3 obtained

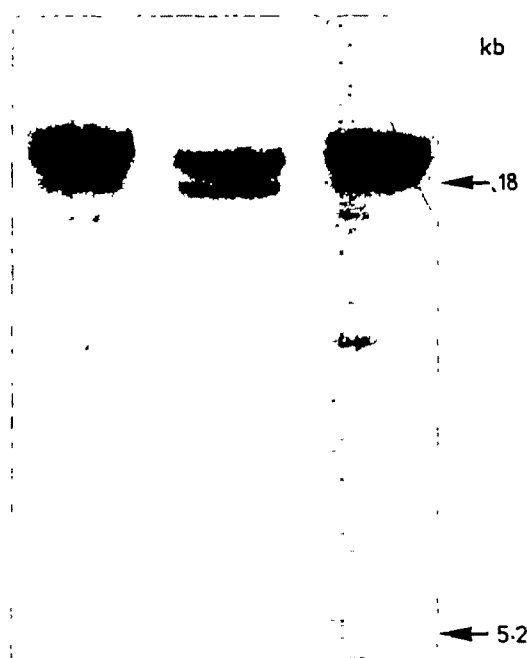


Fig 3 Southern blot analysis of *Bam* HI digested DNA hybridized with OTC cDNA. Band sizes are given in Kb. Polymorphic sites are illustrated by arrows.

her haplotype 1 from her (unaffected) father. In this eventuality diagnosis could have been offered.

KINDRED D

The only known heterozygote for ornithine transcarbamylase deficiency in this family, II 2, had haplotype 2,5. Her mother and sister also had these haplotypes and her father and her unaffected brother had haplotype 5. Protein loading tests in both the mother and the sister were negative. Thus it was not certain whether the propositus's carrier state was the result of a new mutation or whether her mother and sister were also carriers. Had her sister inherited haplotype 5 from her mother instead of haplotype 2, then heterozygosity could confidently have been excluded. The information obtained, however, made it certain that as far as ornithine transcarbamylase was concerned her genotype was the same as her mother's. Either both were carriers or both were normal, and this affected genetic counselling about risk rates.

KINDRED E

The propositus's mother (II 2) was a carrier for ornithine transcarbamylase deficiency as she had given birth to two sons with presumed ornithine transcarbamylase deficiency and had a positive protein loading test. DNA analysis showed that she and her two sisters had haplotypes 1,5, her mother had haplotype 5,7, and her father had haplotype 1. As all three sisters and their mother had had positive protein loading tests all were presumed to be carriers. The defective gene in this family was linked to haplotype 5, because the sisters' father, who was healthy, had haplotype 1. Thus prenatal diagnosis could be offered to all three sisters.

KINDRED F

II 1 had haplotype 1,1 and thus it was not possible to distinguish between her two X chromosomes using only *Msp*I and *Bam* HI. No prenatal diagnosis was possible for her at the time of writing.

A change of a *Taq* I restriction endonuclease site in two families with ornithine transcarbamylase deficiency was recently described, which could represent a new mutation or another polymorphism.⁸ Because the restriction fragment length polymorphisms for *Msp*I and *Bam* HI were uninformative in two kindreds (B and F) we investigated two carriers (kindred B (II 2) and kindred F (II 2)) for the presence of these *Taq* I sites, no changes were found. Further, no change in the *Taq* I sites in carriers from two other families (kindred A (II 2) and kindred C (II 2)) were found. In addition, a *Taq* I polymorphism characterised by a 3.7 and 3.6 kb

band has been described.¹⁴ We have had no success in finding this restriction fragment length polymorphism in carriers from four kindred with the deficiency (A, B, C, and F) nor in 20 control female subjects.

Discussion

In this paper we describe the investigation of six kindreds of patients with ornithine transcarbamylase deficiency using a cDNA probe for the ornithine transcarbamylase gene, and illustrate the principles and problems of this type of analysis.

Before the availability of cDNA probes prenatal diagnosis of ornithine transcarbamylase deficiency could only be attempted by diagnosing sex and then terminating pregnancies with a male fetus (50% of which would probably be unaffected),¹ or by examination of a fetal liver biopsy specimen,¹⁵ which is not always possible. Prenatal diagnosis by direct gene analysis was first achieved by Old *et al*, who excluded ornithine transcarbamylase deficiency in a male fetus from a family in which karyotyping had established the presence of a deletion.⁷

Where there are no deletions, the disorder can be detected by establishing a linkage between the mutant ornithine transcarbamylase gene and restriction fragment length polymorphisms in or around the gene. Rozen *et al* reported that a combination of restriction fragment length polymorphisms observed with *Bam* HI and *Msp*I could be expected to be informative for 80% of women at risk.⁶

For linkage studies to be helpful for prenatal diagnosis of an X-linked disorder such as ornithine transcarbamylase deficiency, there are certain prerequisites. Firstly, the mother must be a known carrier of an ornithine transcarbamylase mutation and a heterozygote for a restriction fragment length polymorphism. Secondly, there must be either DNA available from at least one son, affected or unaffected, or the mother's mother must be a known carrier, and DNA must be available from the mother's father or a brother. A known carrier of an ornithine transcarbamylase mutation is defined as either an obligate carrier on family history or a subject shown to be a carrier by the results of a carefully controlled protein loading test. When all this information is not available it may be possible to make an exclusion diagnosis in a proportion of cases, but prenatal diagnosis cannot unequivocally be offered.

In the kindreds we studied DNA was not available from any of the affected deceased sons. In kindreds A and E information from a combination of both the DNA and protein loading studies made prenatal diagnosis available for the mothers of affected sons.

as well as for two daughters in kindred A and two sisters in kindred E. The information from protein loading tests enabled these family members to be classified as carriers, and the DNA study showed that the X chromosome could be successfully tracked. This was possible in kindred E because DNA was available from the father of the three sisters, and their mother was known to be a carrier from a protein loading study.

In the other four kindreds prenatal diagnosis could not be offered to the mothers of affected boys, either because they were not heterozygous for any detected restriction fragment length polymorphism (kindreds B and F) or because DNA from affected or unaffected sons was unavailable, in addition to the uncertainty about whether these mothers were carriers as a result of a new mutation. Nevertheless, diagnosis by exclusion might have been possible in some of these families if their haplotypes had been different as illustrated by the results for kindred D, but in no case was this so.

The current study indicates two important points. Firstly, DNA diagnostic tests may be successfully complemented by conventional biochemical techniques. Another example is the use of creatine kinase measurements in defining carrier states in Duchenne type and Becker's muscular dystrophy.¹⁶ Secondly, it is vital that tissue or DNA itself should be collected and stored from any patient with an inherited disorder who seems likely to die. It is crucial that paediatric and obstetric units obtain a protocol from their regional molecular biology service so that such collections can be made at any time.

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Cost of neonatal care

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SUMMARY A six month evaluation of the costs of a regional neonatal medical and surgical unit was carried out. The total cost for six months was £970 000 and this covered 4349 inpatient days and 282 admissions. For medical cases the cost ranged from £132 to £27 600 and the mean daily cost for different weight groups ranged from £159 to £274. The average daily cost for regional patients at £258 was greater than for district patients who cost £199. Altogether 23 medical patients weighing less than 1000 g at birth were admitted. The total cost for nine of these infants who died was £30 991—about 3% of the unit's total budget.

It is widely accepted that improvements in neonatal care and in particular the provision of intensive care facilities has reduced mortality in preterm infants.¹ Surprisingly little, however, is known about the financial costs of such treatment. In the United Kingdom there have been only two comprehensive studies that have assessed the economics of neonatal intensive care.^{2,3} When in 1984 a new mixed medical and surgical neonatal unit was opened in this hospital an evaluation officer (AS) was specifically appointed to study the cost of running the unit. We believe that there is a need for more information concerning the economics of neonatal care if known deficiencies in the allocation of resources are to be corrected.

Methods

This evaluation was carried out on the neonatal unit of the General Infirmary at Leeds, this is a regional referral centre for both medical and surgical admissions. There are roughly 48 000 deliveries per year in the Yorkshire region with about 4500 births per year in this hospital. Within the neonatal unit there is a surgical area (10 cots), an intensive care area (six cots designated for ventilation), and a special care baby unit (20 cots). Although there are many occasions when more than six babies receive intensive care, the nursing establishment is based on these figures. In addition to admissions from our own delivery suite (including in utero referrals) there is also a 'flying squad' that transfers outborn referrals requiring intensive care.

In 1985 an evaluation officer (AS) was appointed for six months (February to July inclusive) with the

aim of providing an accurate prospective assessment of the costs of running this unit. Infants have been divided into regional referrals (outborn and in utero transfers) or district admissions and also into medical or surgical admissions. Surgical patients included both patients born in this hospital and those transferred from regional hospitals with primary surgical problems. Their medical and surgical care was provided by the surgical team, but not all infants required surgery. Unlike the district cases the cost for regional referrals does not represent their true total hospital cost because of the continuing need for special care once they are discharged back to their referring hospital. The three main areas of cost identified were:

(1) DIRECT TREATMENT COSTS

Direct treatment costs comprised the salaries (at 1984 pay award levels) for the medical nursing, and other professional staff (for example, medical physicists and pharmacists), and also the cost of supplies and equipment including replacement, repair, depreciation, and maintenance. For each patient costs were calculated on a day to day basis. Each patient day was allocated to one of three categories: intensive care, where patients generally required respiratory support (ventilation or continuous positive airways pressure) and were subject to intensive care staffing levels; special care, which included babies discharged from intensive care and preterm babies awaiting discharge home; and surgical care. For each of these three categories nursing costs were allocated in proportion to rostered staffing levels for each category. Medical staffing costs were apportioned according to indi-

vicinal doctors' clinical responsibilities for daytime and on call periods.

(2) PATIENT TREATMENT COSTS

Patient treatment costs included the costs of drugs, intravenous feeding solutions, investigations by the pathology laboratories (chemical pathology, haematology, and microbiology), blood transfusions, radiology, and operating theatre time. Maternal care for regional referrals where appropriate was included in this category. A simple average daily cost was chosen for maternal care as a more accurate figure could only be obtained by a similarly detailed study of obstetric costing. The cost of the mothers' care was met from the obstetric budget. Care given to the infant by the mother did not result in any reduction in nursing costs for that infant because of the continued nursing supervision usually required.

(3) GENERAL SERVICE COSTS

The general service costs reflected the general running costs of the hospital such as payment to ancillary staff (for example, porters, cleaning staff, etc), services, power, heat and lighting. Altogether 32% of the hospital's budget was in this category and that of the neonatal unit was calculated as an additional 32% of its budget. Figures for the costs (at 1985 prices) were supplied by the district finance officer and a record of all consumables used was available during the time of the evaluation. Each department within the hospital was, where necessary, asked to provide costs for each item of service.

For each admission a careful record was kept of the number of days spent on the unit. All investigations, including x radiography and blood transfusions, were tabulated as well as the days of intravenous feeding and drug treatment (A fuller account of the costing method is available from the authors.)

All prices quoted are at 1985 levels.

Results

Over the six month period there were 282 admissions with a total of 4349 inpatient days on the neonatal unit (table 1). Medical patients were

Table 1 Admissions and (inpatient days) during the six month evaluation

Admissions	Medical	Surgical	Total
District	119 (1594)	22 (283)	141 (1877)
Regional	71 (1373)	70 (1099)	141 (2472)
Total	190 (2967)	92 (1382)	282 (4349)

large-y preterm infants suffering from respiratory and other complications. Surgical patients consisted large-y of those with malformations and those with surgical complications of prematurity (for example, necrotising enterocolitis). Included in these figures were seven admissions to the unit who despite being older than 4 weeks required the specialised care available on this unit. They were included for complete accuracy. They spent a total of 23 inpatient days at a total cost of £6000.

During the evaluation period direct treatment costs amounted to £556 000 (table 2). When this was allocated to each area of care and then divided by total inpatient days for that area the daily direct treatment cost could be calculated: intensive care £294 per day, special care £89 per day, and surgical care £125 per day. The estimated cost for each facility, used in the category of patient treatment costs and the total cost to the newborns' unit of these facilities is shown in table 3. Patient treatment costs were £104 000 in total. The general service cost for the unit for the six month evaluation was estimated at £312 000. When these two additional elements of cost were included the average charge for intensive care was £467 per day while for special care it was £166.

The analysis of cost for district and regional

Table 2 The breakdown of direct treatment cost

Category of cost	Cost in £000's per six months (%)
Medical staff	72 (13)
Nursing staff	330 (59)
Other staff	19 (3)
Supplies/equipment	110 (20)
Repair/maintenance	25 (5)
Total	556 (100)

Table 3 Breakdown of the patient treatment costs and approximate cost for each category

Facility	Total cost for six months (£)	Cost per unit (£)
Intravenous feeding	5 900	10 per day
Intravenous drugs	1 300	1 per day
Chemical pathology	7 100	5 per day
Microbiology	2 600	4 per request
Haematology	6 600	5 per request
Group/serum	2 100	9 per request
Blood/plasma	5 000	20 per unit
Ultrasound	4 400	39 per scan
x Radiography	7 300	27 per film
Maternal inpatient care	22 000	123 per day
Operating theatre	1 600	144 per hour

Table 4 Patient numbers, duration of stay, and costs (£) for neonatal medical patients

	Birth weight			
	≤1000 g	1001–1500 g	1501–2500 g	>2501 g
<i>District patients</i>				
No of patients	6	18	42	49
Average stay (days)	48	36	11	3
Average cost/case	10 300	8 100	1 800	600
Average cost/day	213	224	159	187
Average range of costs/case	621–27 600	490–18 300	132–10 900	139–3 500
<i>Regional patients</i>				
No of patients	17	22	23	6
Average stay (days)	26	20	19	8
Average cost/case	6 700	5 300	4 600	2 700
Average cost/day	258	270	246	274
Average range of costs/case	444–21 900	564–22 750	445–15 300	851–5 700

Table 5 Patient numbers, duration of stay, and costs (£) for surgical patients

	Origin	
	District	Regional
<i>Birth weight ≤2500 g</i>		
No of patients	6	31
Average stay (days)	16	16
Average cost/case	3 350	3 650
Average cost/day	214	227
<i>Birth weight >2500 g</i>		
No of patients	16	39
Average stay (days)	12	16
Average cost/case	2 400	3 250
Average cost/day	202	209

medical admissions and for surgical admissions are shown in tables 4 and 5. Over a six month period the total running costs of a combined medical and surgical unit amounted to £972 000: this is the equivalent of £1.94 million per year. This cost was divided roughly into equal thirds for district medical, regional medical, and surgical groups. Although our analysis dealt with a six month period, there was a total of 560 admissions over the whole of 1985 so the assumption that a six month period would be representative of the unit's workload was correct.

Discussion

While it is widely accepted that the provision of neonatal intensive care has been associated with an improved survival for very low birthweight babies,¹ only two studies have comprehensively investigated the costs of such care in the United Kingdom.^{2,3} The total cost for 119 district and 71 regional medical patients was similar: £320 000 and £350 000, respec-

tively, with the average cost for regional patients being £5000 compared with £2700 for district patients. This is due to the longer average stay (19 days against 13 days) for regional patients and their greater average daily cost. The above trends are reversed if we consider only the 63 very low birthweight babies admitted who constituted 57% of regional and 21% of district admissions. The district admission babies stayed longer on average (39 days compared with 22 days for the regional patients) and cost £8700 per admission while regional infants cost £5900. The shorter stay for regional babies was because they could be transferred back to their referring hospital to complete their care. The longer average length of stay for regional medical patients weighing >1500 g (17 days) compared with equivalent district patients (seven days) occurred for two reasons: (a) the district patients could complete their hospital care on our transitional care unit and, (b) regional admissions of this weight represented a selected group of very ill patients.

The average daily cost of care varied between £187 and £274 for medical patients. The regional admissions required more intensive care (26% of inpatient days) than district cases (17% of inpatient days). This was probably a reflection of the greater number of very low birthweight babies among the regional admissions. Maternal care for mothers transferred with their baby amounted to a total of £20 000 and contributed £14 on average to the daily cost of regional medical patients.

The ethical and economic aspects of the care of the most immature infants (less than 1001 g birth weight) merit, and have received, recent discussion.^{4,5} Our study showed that of 23 such babies nine died: five on day 1, three more by day 3, and one at 44 days. The average cost for their care was £3443, but actual costs ranged from £498 to £21 859 and for

Table 6 Comparison of estimated costs (£) for three recent British costing studies (and financial year)

	Birmingham 1984*	Liverpool 1984	Leeds 1985
Average cost/day			
Care level			
High	281	297	467
Intermediate	146	158	} 166
Low	51	71	
Babies of very low birth weight			
Cost/patient	4850	4159	6979
Cost/survivor	6220	4450	8192
Cost/non-survivor	1081	3446	4169

*Birmingham study undertaken in 1981. Figures converted to 1984 levels by Sandhu *et al.*³

these nine babies totalled £30 991; this is about 3% of the unit's total expenditure.

Direct treatment costs for medical patients were calculated for two levels of care only—intensive and special care. Intensive care in this study was broadly equivalent to that in other studies,^{2,3} but our special care also included high dependency or intermediate care as described in these studies. The special care area studied here formed a continuum of the levels mentioned above and staffing costs cannot be broken down further. A transitional care unit in this hospital provides special care facilities on postnatal wards for a large number of babies born between 30 and 35 weeks' gestation. Therefore our special care unit may not be directly comparable with others.^{2,3} It was also decided not to allocate specific equipment costs to various levels of care as it was felt that, as equipment is often not in use, its costs should be borne by those who used it and by those who had access to it if required. Table 6 shows the comparison between this study with those from Birmingham¹ and Liverpool.² These studies were broadly similar despite being conducted in different financial years

and using different methods. Our analysis clearly shows that the major cost incurred in treating very low birthweight babies is staff salaries. Additional patient treatment costs (table 3) are minor but hospital overheads make an important contribution to the total cost of care.

We believe that funding for neonatal care should be based on demonstrated costs. As the future direction of finance within the National Health Service is likely to be based on the concept of semiautonomous budgeting for individual units within hospitals it is important that such budgets should be based on accurate costing information. Furthermore if regional centres are to continue to develop and flourish then appropriate funding must be forthcoming. This should be related to numbers of patients treated rather than by funding intensive care costs that may not reflect the workload.

Dr S Ryan is sponsored by the Special Trustees of the General Infirmary at Leeds

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Short reports

Immediate effects of albumin infusion in ill premature neonates

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SUMMARY Ten normotensive premature infants with idiopathic respiratory distress syndrome, and albumin concentrations of less than 30 g/l were given 5 ml/kg of 20% salt poor albumin by infusion. Concentrations measured six hours after infusion had increased significantly and these were associated with significant reduction in weight and improvement in urine output.

Sick premature infants are often oedematous in spite of being hypovolaemic.¹ It is likely that this is a consequence of hypoalbuminaemia because leaks of protein have been described in neonates with respiratory distress,² possibly as a result of the high histamine concentrations that affect capillary permeability.³ In such infants hypotension has been effectively treated by infusions of albumin, which have been associated with improvement in colloid osmotic pressure, circulating plasma volume, and glomerular filtration.^{1 4}

The present study was designed to find out whether infusions of albumin were effective in treating hypoalbuminaemia in normotensive sick infants

Patients and methods

Infants less than 2 weeks of age, except those receiving peritoneal dialysis and those with chest drains in situ (both of which interfere with weighing) were eligible for the study. Babies given albumin infusions for the emergency treatment of hypotension were also excluded.

Ten infants entered the study. Their mean birth weight was 1390 g (range 560–3315 g) and mean gestational age 29 weeks (range 24–36). The post-natal age at the time of infusion ranged from 24 hours to 5 days, mean age 1.7 days. All had a clinical diagnosis of respiratory distress syndrome and were receiving artificial ventilation by a Sechrist ventilator. They were ventilated at peak inspiratory pressures ranging from 14–32 cm H₂O. Five of the

infants were paralysed before and during the study. All 10 infants had albumin concentrations of <30 g/l, with peripheral oedema.

The content of fluid to be given to each baby was decided daily. On the first day 40 ml/kg were given and this amount was not increased if the infant gained weight during the first three days.

Urea, electrolytes, and albumin concentrations were measured daily in all babies, and infants who were hypoalbuminaemic (<30 g/l) were entered into the study. A solution of 5 ml/kg/20% salt poor albumin was then infused, and the volume subtracted from the total daily fluid requirement. Before the transfusion and at the end of the six hours after it the infant was weighed, and urea, electrolytes, and albumin concentrations measured again. For six hours before and after the infusion urine output was measured. Manual expression was not used and urine was collected that had been voided spontaneously in the two six hour periods.¹ During a similar period blood pressure was recorded hourly as the mean of the systolic and diastolic pressures using an intra-arterial transducer, and reported as the average for each six hour period.

During the 12 hours of the study period no other alteration was made in the infant's fluid input, nor was there any change made in the type of incubator or the use of overhead heaters. Twelve hours was chosen as the study period as it was the longest over which the fluid intake of sick infants on ventilators could be guaranteed to be constant. Treatment with phototherapy was recorded.

To assess any effects of the albumin infusion, albumin and electrolyte concentrations, blood pressure, weight, and urine output were compared before and after the infusion.

Ethical permission was granted by the hospital ethical committee.

The significance of differences before and after albumin infusion were assessed by the paired Student's *t* test.

Results

No changes were made in the quantity of fluid or the

Table Measurements before and after infusion of albumin in 10 infants. Figures are given as mean (range)

	Before infusion	After infusion
Albumin (g/l)	27 (21-30)	32 (29-36)
Weight (g)	1534 (734-3210)	1363 (776-3094)
Urine output (ml/6 hrs)	11.5 (1.3-23)	2.2 (0.7-37)
Blood pressure (mm Hg)	35.1 (28-62)	33.5 (30-56)
Sodium (mmol/l)	133 (131-149)	139 (130-149)
Urea (mmol/l)	5.8 (0.7-10.1)	5.5 (0.8-9.7)

amount of phototherapy given to any infant during the period of the study. There were no significant changes in the urea and electrolyte concentrations or in the blood pressure readings after the albumin infusions (table). Albumin concentrations rose ($p < 0.01$) and weight decreased significantly in all 10 infants ($p < 0.01$). The mean urinary output of the study group increased following infusion ($p < 0.05$), but in two infants it decreased (20 to 15.4 ml and 1.3 to 0.7 ml, respectively). Though no positive correlation was found between peak inspiratory pressure at the start of the study and the response to the albumin infusion, the two infants whose urinary output decreased were both paralysed and had severe respiratory distress syndrome (peak inspiratory pressures 26 and 32 cm H₂O respectively).

Discussion

The concentration of albumin of < 30 g/l that we used was considerably lower than that used in a previous study,¹ but was the lowest concentration of albumin recorded in the first 24 hours of life in a group of 50 infants treated in our neonatal intensive care unit whose gestational age was > 28 weeks.

Albumin given to normotensive infants with hypoalbuminaemia increased circulating albumin levels, and this was followed by improvement in urinary output, reduction in weight, and a subjective decrease in peripheral oedema. In two infants whose urinary output decreased slightly despite increased albumin concentrations weight loss did occur and may therefore have reflected an increased insensible water loss. Though this occurred in two paralysed infants with severe respiratory distress syndrome which may in itself have influenced urinary output, infants in a similar clinical condition did increase their urine output in response to the albumin infusion. This difference may be explained by our method of urine collection. Urine was only measured after it had been spontaneously voided, and incomplete bladder emptying may have occurred in the two paralysed infants. The clinical policy of

our unit, however, is not to express the bladder if the infant is passing urine and we felt that it was important that this practice should not be altered.

In infants with the respiratory distress syndrome a diuresis has previously been associated with improvement in respiratory function.⁵ Theoretically an increase in the colloid osmotic pressure resulting from the albumin infusion could reduce pulmonary oedema and have a similar effect, but this has so far not been proved.⁴ It is possible that replacement of albumin might aggravate leaks of protein but in our study serum albumin concentrations six hours after infusion remained raised, suggesting that this was either not the case, or if it was that the leak was gradual.

In a previous study only a poor correlation was found between the degree of oedema and concentration of albumin.⁶ In that study, however, the infants were suffering from a variety of disorders and were of different postnatal ages, so in such a heterogeneous group there could be several explanations for the oedema. The present report described a group of infants with similar respiratory problems and management, in whom low albumin concentrations were associated with oedema that lessened after infusion of albumin. This clinical observation was supported by the significant weight loss.

We conclude that in these normotensive infants who were in the acute phase of the respiratory distress syndrome, albumin infusions do improve urinary output.

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Commentary

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Most infants born before 36 weeks' gestation have a serum albumin concentration below 30 g/l, this is a concentration which in a child or adult would be classed as hypoalbuminaemia.¹ Most of these infants have varying degrees of oedema too, but there is poor correlation between serum albumin concentration and the amount of oedema, and neither relate well to the presence or absence of respiratory disease. The implication is that hypoalbuminaemia is normal for the preterm infant, perhaps because the low systemic blood pressure (and therefore the capillary hydrostatic pressure) makes a high colloid osmotic pressure unnecessary. A common finding, however, in a preterm infant is not necessarily normal.

This interesting study by Greenough and her colleagues seems to suggest that hypoalbuminaemia of prematurity is abnormal as albumin infusion is associated with a diuresis, weight loss, and possible reduction of oedema. These are the findings one would expect from the infusion of albumin into a child with the nephrotic syndrome. Disappointingly though, the study lacks a control group of infants with respiratory distress who did not receive albu-

min. This means that the association might be a chance one, with the change in urine output and weight being related to time rather than albumin. Most preterm infants studied at this age would be in the process of losing up to 20% of their birth weight, at least in part via their urine output. Alternatively, the association might be causal, but unrelated to hypoalbuminaemia—albumin infusion might act as a mild diuretic by increasing renal blood flow.

Before neonatologists reach for the albumin bottle to treat this 'disease', we need to know more. Is it albumin infusion that is responsible for the diuresis? If so, is it temporary and does the fluid soon reaccumulate? More importantly, does it improve the infant's respiratory disease? Furosemide, which produces a much more impressive diuresis and weight loss has not been shown to alter the course of respiratory distress syndrome.²⁻⁴

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Management of uncomplicated meconium ileus with T tube ileostomy

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SUMMARY Five neonates with uncomplicated meconium ileus were successfully managed by laparotomy and T tube ileostomy. This method seems to offer advantages over other surgical techniques used in the management of uncomplicated meconium ileus that fails to respond to decompression by Gastrografin enema.

Since Haatt and Wilson's first description of the successful surgical management of meconium ileus in 1948,¹ improvements in the surgical care of neonates, together with a variety of techniques to

deal with the intraluminal obstruction, have led to greatly improved survival rates.^{2,3} Improved dietary and medical management have also given more hopeful long term prognosis.^{4,5} T tube ileostomy as advocated by Harberg *et al*,⁶ seems to offer important advantages over surgical techniques previously described for the management of uncomplicated meconium ileus that fails to respond to decompression by sodium meglumine diatrizoate (Gastrografin) enema.

Patients and methods

Since 1982 five neonates have been admitted to the

Red Cross War Memorial Children's Hospital, Cape Town, with uncomplicated meconium ileus. In three, unsuccessful attempts were made to relieve the obstruction by Gastrografin enemas. After the diagnosis had been confirmed at laparotomy, a 14F T tube catheter with multiple holes cut in both limbs was prepared, each limb being 3 to 4 cm long. The tube was inserted through an enterotomy into the dilated and hypertrophied ileum about 3 cm proximal to the distal narrowed segment, and secured with a double purse string suture. It was immediately irrigated with saline and 5% acetyl cystine or Gastrografin to loosen the compacted distal inspissated pellets and proximal viscous meconium. The T tube was brought out through a stab incision in the right iliac fossa and the enterostomy was secured to the anterior abdominal wall. Starting the day after operation the T tube was gently irrigated twice daily with a solution of 5% acetyl cystine or diluted Gastrografin until complete decompression had been achieved. Parenteral nutrition was given until normal bowel function had returned, after which replacement of pancreatic enzymes was introduced orally and milk feeds were started. The T tube was removed 18–21 days after the operation.

Results

All patients survived without morbidity (table). Spontaneous closure of the fistula occurred within two days in all five, and one patient developed a small granuloma which responded to application of caustic. Full bowel function had returned in all

infants by the tenth postoperative day. There were no adverse long term sequelae noted at follow up examination six months to five years later. One patient required laparotomy for obstruction by inspissated stools and adhesions at the age of 2, but the area of the T tube ileostomy was not responsible for the obstruction. All five have developed pulmonary signs of cystic fibrosis, but are progressing well.

Discussion

Meconium ileus is a comparatively infrequent cause of intestinal obstruction in neonates. Referral is usually delayed and obstruction well established at presentation. When complications such as volvulus, atresia, or perforation had been excluded on clinical and radiological grounds an attempt was made to relieve the obstruction by Gastrografin enemas. With terminal ileal obstruction, however, we were unable to achieve satisfactory decompression. Our previous experience with other surgical techniques (table) indicates notable morbidity and mortality.

The use of the T tube has several advantages. The operation is less extensive than others and requires minimal handling of the bowel. Resection of the distended but viable segment of ileum is not necessary and there is no intraperitoneal suture line. Immediate postoperative irrigation may be performed safely and the T tube may be removed by simple extraction when appropriate. Spontaneous closure of the fistula occurs rapidly. We therefore recommend this operation for uncomplicated meconium ileus when Gastrografin enemas have failed to alleviate the obstruction.

Table Surgical management of meconium ileus in 17 neonates* 1967–1986

Operation	No of cases	Morbidity and mortality
Distal chimney enterostomy with resection	10	Sepsis at ileostomy site (n=4) Formal closure required (n=9) Second attempt at closure required (n=3) Intraperitoneal leak and death (n=1)
Proximal chimney enterostomy with resection	1	Formal closure required
Resection with primary anastomosis	1	Adhesive bowel obstruction when 10 months and 21 months old, died after second laparotomy
T tube ileostomy	5	None

*Several Gastrografin enemas failed to relieve the obstruction in four

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Diarrhoea due to breast milk: case of fucose intolerance?

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SUMMARY An unusual form of diarrhoea is reported that was relieved when breast feeding was stopped. Chromatography to estimate sugars in the faeces should be performed for all infants with unexplained diarrhoea before changes are made in the diet.

Diarrhoea in breast fed infants is rare. We describe an infant who had severe diarrhoea when breast fed but who was not intolerant of lactose

Case report

A first born baby girl was delivered normally at term weighing 3370 g. She was entirely breast fed, but passed profuse watery yellow stools up to five times a day from the age of 1 week and though weight gain was always satisfactory this necessitated admission to hospital. No bacterial or viral pathogens were isolated from the stools, but they contained a reducing substance that was subsequently identified by paper chromatography as fucose.¹ Polymers containing fucose were also seen, and the pattern of oligosaccharides was similar to that found in human milk. Breast feeding was stopped and Pregestemil was substituted for a short time; thereafter she was fed on SMA (Wyeth). The diarrhoea has not recurred, and she remains well at the time of writing. There was no relevant family history.

Discussion

Human milk is a rich source of oligosaccharides, in contrast to cows' milk that contains only the disaccharide lactose in a concentration of 46 g/l. About 25 oligosaccharides have been detected in human milk with a total concentration of about 18 g/l,² and some of their structures have been described.³ In contrast the concentration of lactose in human milk is about 70 g/l.⁴ Free fucose (6-deoxy-L-galactose) does not occur in human milk, but it is a constituent of several oligosaccharides that do occur in concentrations of about 1.3 g/l.

Unexplained diarrhoea in a new born breast fed infant in association with the finding of a reducing substance in the stools suggested a diagnosis of

congenital lactose intolerance (lactase deficiency). This is usually treated by feeding with a milk free of lactose, and the life long exclusion of cows' milk products from the diet. The avoidance of lactose would have been unnecessary for this infant. In the light of our experience with this infant, and of two others known to one of the authors (JS), we suggest that sugar chromatography should be carried out on the stools of all infants with unexplained diarrhoea before changes are made in the diet.

The mechanism of the diarrhoea is not clear. It is possible firstly that fucose liberated from oligosaccharides was not absorbed, and diarrhoea ensued in a way similar to that in glucose galactose malabsorption. Secondly, it may be that the infant lacked the appropriate enzymes to hydrolyse these oligosaccharides, again resulting in an osmolar diarrhoea. Bacterial hydrolysis of these oligosaccharides in the large bowel would release fucose, which would not be absorbed from the bowel itself, and the fucose could therefore be identified on the chromatogram. In the absence of further studies, however, it is not possible to be certain.

Counahan and Walker-Smith found oligosaccharides in the stools of five of 51 infants tested, four of whom were breast fed.⁵ These oligosaccharides were not characterised. Because oligosaccharides occur in breast milk it seems unlikely that the oligosaccharides in the stools were entirely of bacterial origin as these authors suggest.

This type of intolerance to human milk is rare, and we could find no previously published reports.

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Hypercalciuria as a cause of persistent or recurrent haematuria

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SUMMARY Of 91 children with idiopathic persistent or recurrent haematuria, eight also had hypercalciuria. This was transient in three and persistent in five. Persistent hypercalciuria was a rare cause of microscopic haematuria (two of 30), but common in association with gross haematuria (three of 11).

Hypercalciuria has been reported as causing haematuria, both gross and microscopic, in the absence of diagnosable calculi.¹⁻⁵ Stapleton *et al*⁶ described 23 cases of hypercalciuria in 83 children being investigated for idiopathic haematuria (microscopic and macroscopic) over a two year period. In 23 children a renal or urological cause was found; 22 of the remaining 60 children had hypercalciuria. Of 37 children with gross haematuria, 16 had hypercalciuria. As these findings do not accord with our experience, we report a series of 91 patients.

Patients and methods

During the period 1979-85 we saw 91 children aged from 2 to 15 years with persistent or recurrent haematuria in whom no renal or urological cause could be found. Kidney biopsies were not performed. Patients who had protein in the urine were excluded, as were those with other diseases or with a previous history of stones in the renal tract. Forty children were seen at the Assaf Harofeh Hospital and 51 at the Beilinson Medical Centre. Eleven patients (six and five at the two hospitals, respectively) had at some time had gross haematuria.

A 24 hour urine specimen was obtained from all patients under normal home conditions and without dietary modification. Hypercalciuria was diagnosed as a calcium:creatinine ratio of over 0.6:1, this representing the ninety eighth centile calculated for 131 healthy children studied by one of us (M Tieder, unpublished observation). This reflected a calcium excretion of greater than 0.1 mmol/kg/24 hours. Whenever a value of greater than 0.6 was found at least two further urine collections were obtained.

The concentrations of calcium and creatinine in the urine were measured by the Technicon auto-analyser at the Beilinson Medical Center. At the

Assaf Harofeh Hospital, the calcium concentration was measured manually by atomic absorption spectrophotometry and the creatinine concentration by the alkaline picrate reaction. In six urine specimens examined in both laboratories, concentrations of calcium and creatinine, and the calcium:creatinine ratio were almost identical, the mean (SD) difference in calcium:creatinine ratio being 0.04 (0.02).

Results

Eight of the 91 patients with haematuria also had hypercalciuria on a single estimation. Repeat urine collections confirmed persistent hypercalciuria in only five of these children, in three calcium excretion having returned to normal. Three of the patients with hypercalciuria had gross haematuria at some time, and two of the three later developed renal calculi. The remaining patients have been followed up on treatment for two to six years, and have not developed calculi. All five of these children have at least one parent with hypercalciuria.

Mean (SD) calcium:creatinine ratio in the urine of the 83 patients who did not have hypercalciuria measured from a single urine collection, was 0.25 (0.17) compared with 0.28 (0.17) in 131 healthy children. Thus haematuria does not seem to be associated with higher calcium excretion except in these subjects with pronounced hypercalciuria.

Discussion

In our series about 9% of the children with persistent or recurrent haematuria had hypercalciuria (that is, a calcium:creatinine ratio more than two standard deviations above the mean for our healthy childhood population) when a single 24 hour urine specimen was tested. It is difficult to explain the difference between these findings and those of Stapleton *et al*⁶ who found hypercalciuria in 37% of all children with unexplained haematuria and in 15% of those with microscopic haematuria. The authors of that paper believe that urolithiasis is more prevalent in their population than in other regions. Unfortunately they did not compare calcium excretion in the urine of children with haematuria with that of normal children, and they

diagnosed hypercalciuria on the results of testing a single urine collection. We believe it is important to record persistent hypercalciuria by testing repeated urine collections, as a single collection may be misleading.

The fact that two of our five hypercalciuric patients (both of whom had had episodes of gross haematuria) went on to develop calculi suggests that such patients should be treated. As idiopathic hypercalciuria is a lifelong, usually asymptomatic condition such treatment should probably be limited to recommending a diet low in calcium and ensuring that even patients who have never shown any evidence of stones in the renal tract should drink enough fluid.

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Pulmonary interstitial emphysema: selective bronchial occlusion with a Swan-Ganz catheter

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SUMMARY A 26 week preterm infant ventilated for hyaline membrane disease developed severe pulmonary interstitial emphysema with extensive right sided bullous formation, mediastinal shift, and subsequent left sided atelectasis. A paediatric Swan-Ganz catheter was used for selective bronchial occlusion with dramatic improvement in the infant's clinical condition and radiographic findings.

Pulmonary interstitial emphysema (PIE) occurs as a complication of mechanical ventilation in infants with underlying hyaline membrane disease. The use of high peak ventilatory pressures with resultant barotrauma leads to extrapulmonary effusions of air along peribronchovascular, pleural, and interlobular passages from ruptured alveoli.¹ The morbidity from the presence of such interstitial gaseous blebs stems largely from hypoxia secondary to a ventilation/perfusion imbalance in an already compromised infant. Accumulation of unilateral interstitial air may also result in bullous air pockets with eventual mediastinal shift and compression of the contralateral lung.

We report our experience with selective bronchial occlusion of the right mainstem bronchus with a Swan-Ganz catheter in a preterm infant with life threatening complications of PIE.

Case report

A girl weighing 760 g was born at 26 weeks' gestation by a vaginal breech delivery with an Apgar score of 5 and 6 at one and five minutes, respectively. The baby required mechanical ventilation almost immediately for moderately severe hyaline membrane disease (inspiratory pressures 14/3 cm H₂O; fractional inspiratory oxygen (FiO₂) 1.0). The initial chest radiograph taken five hours after birth showed early signs of bilateral PIE. At 12 hours of age a right pneumothorax occurred and was drained. Further deterioration in oxygenation necessitated increased ventilation (pressures 22/2 cm H₂O; FiO₂ 1.0). Ventilator support remained unchanged until day 16, when radiographs indicated a worsening PIE that was associated with further hypoxaemia. Stabilisation proved difficult with recurrence of a right pneumothorax after increasing ventilatory pressures to 37/2 cm H₂O; FiO₂ 0.8. Despite dependent positioning of the right emphysematous lung and carefully monitored ventilation, the infant continued to deteriorate.

On day 18 selective intubation of the left mainstem bronchus under fluoroscopy was unsuccessful. The radiographic findings (fig 1) showed large cystic lucencies with hyperaeration and a persistent herniation of the right lung across the midline with mediastinal displacement to the left. At this time the

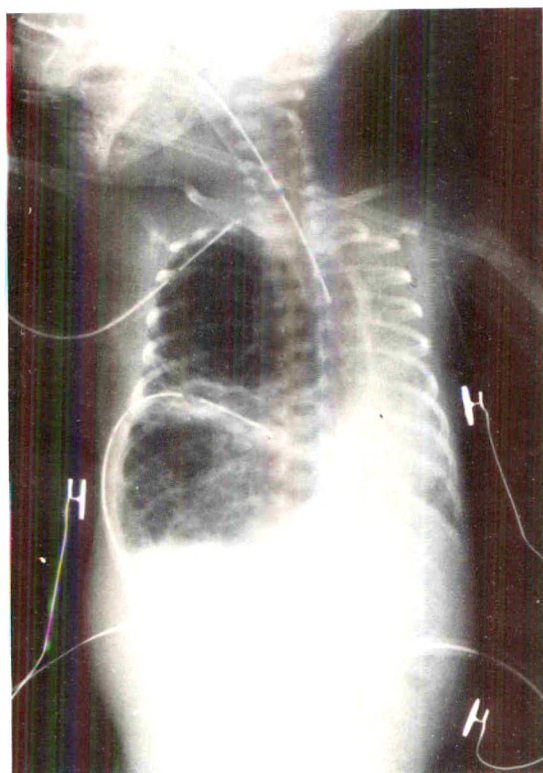


Fig 1 Large cystic lucencies of the right lung with hyperaeration and mediastinal shift to the left side. Two pneumothorax chest drains are shown on the right.

infant developed acute renal failure with intermittent hypotension concurrent with worsening arterial oxygen desaturation (pH 7.17, PCO_2 10.4 kPa, PO_2 5.7 kPa, bicarbonate 28 mmol/l). A decision was made to reattempt collapse of the right lung. This was easily achieved with a Swan-Ganz model 93-117-5 French double-lumen paediatric-flow directed monitoring catheter which was inserted into the right mainstem bronchus with balloon inflation to 0.8 mm diameter. The infant was then intubated with a No 2.5 endotracheal tube that was appropriately positioned above the level of the carina. The procedure was well tolerated and resulted in rapid reduction in inspiratory pressures and improvements in blood pressure, peripheral circulation, and oxygenation (pH 7.39, PCO_2 7.1 kPa, PO_2 7.6 kPa, bicarbonate 32 mmol/l). A chest film three hours later showed atelectasis of the middle and lower lobes of the right lung (fig 2) with a shift of the mediastinum to the midline and re-expansion of the left lung. The Swan-Ganz catheter was deflated intermittently for five minutes

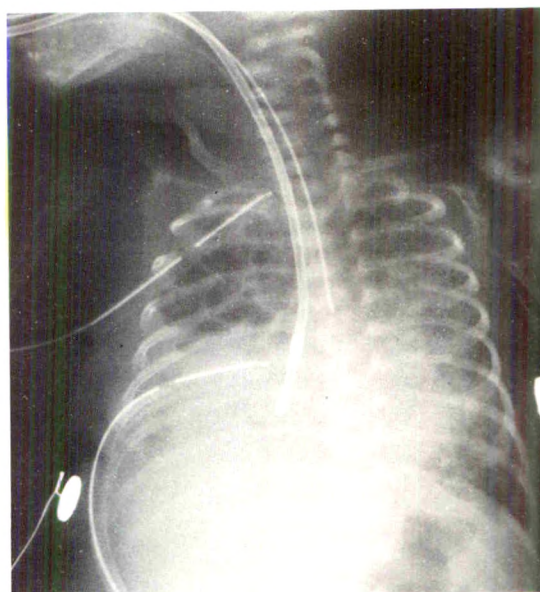


Fig 2 Partial atelectasis of the right lung with Swan-Ganz catheter in place.

every hour, to help minimise bronchial wall pressure necrosis. Forty eight hours later the left lung developed progressive radiological changes of PIE. The Swan-Ganz catheter was deflated for 12 hours and left in situ and then partially reinflated for a further 12 hours before being removed. Gradual re-aeration of the right lung occurred with subsequent bilateral reabsorption of all the PIE. The infant was extubated at 9 weeks of age and has evidence of minimal bronchopulmonary dysplasia.

Discussion

Selective bronchial occlusion has been reported as a successful alternative in the treatment of localised PIE.²⁻⁴ The devices previously used to treat the diseased lung were not without procedural hazard. Mathew and Thach accomplished occlusion of the right mainstem bronchus with an umbilical catheter adapted with a handmade oesophageal pressure balloon,² while DeWitte *et al* used a modified endotracheal tube with an occluded distal end.³ Auerbach *et al* used operative intervention for the insertion of a Fogarty balloon catheter at bronchoscopy in the management of localised cystic PIE.⁴ We chose a Swan-Ganz catheter because it is a safe and reproducible piece of equipment that can be easily inserted without large scale instrumentation that may further compromise the premature infant with PIE. The advantages of our procedure are that:

(1) It is accomplished easily and quickly without fluoroscopy. (2) It comprises simple laryngoscopy with subsequent reintubation of the infant with a 0.5 mm smaller endotracheal tube to permit adjacent placement with the Swan-Ganz catheter. (3) A successful response is seen within half an hour of the procedure with ongoing improvement in the radiological findings. (4) The catheter is radiolucent and clearly marked in 5 cm increments with a sliding gate valve that prevents inadvertent deflation of the balloon. (5) Using a syringe, precise quantitation of the degree of balloon inflation is possible, and although location of the balloon is known (0.9 cm from the catheter tip) its exact position can be determined by insufflating the balloon with dilute contrast fluid. Pulmonary interstitial emphysema should be managed aggressively in the first instance by non-invasive methods. Selective bronchial occlusion utilising a Swan-Ganz catheter provides a

successful alternative measure in severe disease unresponsive to standard treatment.

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Effect of tilting on oxygenation in newborn infants

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SUMMARY Transcutaneous (tc) PO_2 in newborn infants increased on head up tilting (median increase 0.5 kPa at term, 1.0 kPa preterm). Head down tilting was associated with an equivalent fall in tc PO_2 . There was no change in tc PCO_2 . Tilting of infants mechanically ventilated for respiratory distress syndrome or surgery produced no consistent change in PO_2 .

Newborn infants are often nursed on a head up tilt. This study investigated whether a head up or head down tilt produced a change in PO_2 and PCO_2 in healthy prone newborns and in those with respiratory problems.

Patients and methods

Seventeen healthy term infants and seventeen healthy preterm infants (mean birth weight 1300 g) were studied at the Department of Neonatology, Ullevaal Hospital, Oslo. Each term infant lay prone and at least five tilts were performed. Each position: horizontal, 30 degrees head up, and 30 degrees head down, was held for five minutes before the next tilt. The term infants were studied on day one and day

five in active and in quiet sleep. The preterm infants were studied on one day only and tilted 20 degrees head up in their incubators. Transcutaneous PO_2 and PCO_2 were measured in the interscapular region. Values were recorded every 30 seconds. Tilts associated with any body movement or change in sleep state were not included.

To investigate the possibility that tc PO_2 might be influenced by changes in skin circulation from hydrostatic pressure or reflex vasoconstriction due to a baroreceptor response we measured tc PO_2 from two electrodes, one in the intrascapular region and one on the buttock in five infants. Tc PO_2 values from both sites followed each other exactly (fig 1) thus ruling out a gravitational effect on local skin perfusion.

Further studies of PO_2 and head up tilting were carried out in 10 infants receiving intensive care at Hammersmith Hospital, London. Seven of these infants had an umbilical artery catheter with an oxygen electrode at the tip in the descending aorta. The remaining three infants were studied using a transcutaneous PO_2 system.

Results

Fig 1 shows a typical response with PO_2 rising and

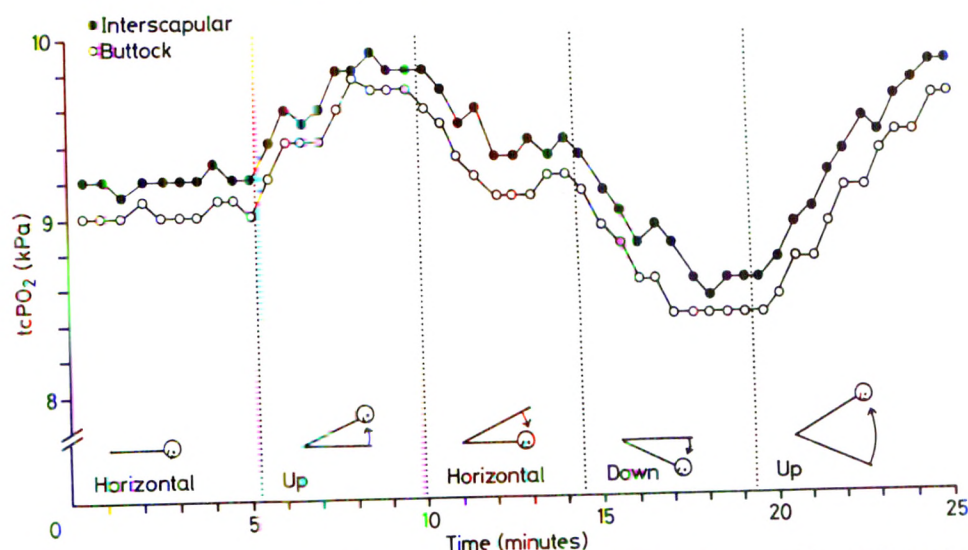


Fig 1 Simultaneous transcutaneous PO_2 measurements from the interscapular site and from the buttock of a healthy full term infant during sequential tilts.

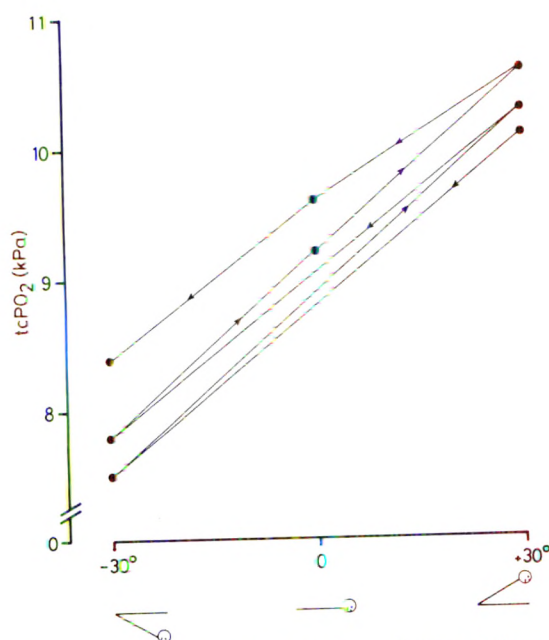


Fig 2 Transcutaneous PO_2 measurements from a full term infant through seven tilts. The sequence is indicated by the arrows.

falling with tilting head up and head down, respectively. In the term infants there was no difference between day one and day five and between sleep states. The median increase in PO_2 on tilting 30 degrees head up was 0.5 kPa (95% confidence

limits 0.2 to 0.8 kPa). The decrease was similar on tilting head down (median -0.6 kPa, 95% confidence limits -0.4 to -1.0 kPa). The increase in PO_2 when tilting from head down to horizontal was the same as when tilting from horizontal to head up. The increase in PO_2 when tilting through 60 degrees from 30 degrees head down to 30 degrees head up was twice the increase observed with a 30 degree tilt (fig 2). These changes in oxygenation were confirmed by pulse oximetry. When tilting head up saturation increased on average by 2%, and it fell by 5% on head down tilt. The preterm infants increased their PO_2 on head up tilting by a median value of 1.0 kPa (95% confidence limits 0.9 to 1.1 kPa) and this was confirmed by arterial PO_2 in one case. Tilting had no effect on $tcPCO_2$.

One preterm infant receiving slow ventilation did show a small rise in PO_2 on head up tilting. None of the six preterm infants receiving mechanical ventilation for respiratory distress syndrome had an increase in PO_2 with head up tilting. The two full term infants, with normal lungs, who were being mechanically ventilated did not show a rise in $tcPO_2$ with head up tilting but did so when off the ventilator and breathing spontaneously.

Discussion

This study has shown that PO_2 in healthy term and preterm newborn infants increases on head up tilting. Tilting head up causes gravity to act on the lower zones of the lungs improving the matching of

ventilation and perfusion and slightly increasing PO_2 .¹ If the above effect were the only explanation one might expect the same or less effect in the preterm infant than in the term infant. The opposite was the case. Tilting presumably reduces the weight of abdominal contents on the diaphragm thus tending to increase functional residual capacity. If the functional residual capacity was not fully stabilised in many preterm infants in the first few days tilting would be expected to have a greater effect on it and on oxygenation in preterm infants than in term infants who stabilise their functional residual capacity early. Improving suboptimal functional residual capacity would increase PO_2 .

The rise in PO_2 with tilting was not found in infants who were receiving mechanical ventilation because of respiratory distress syndrome. This may be due to stiffness of the lungs, pulmonary hypertension, or to the effects of mechanical ventilation. Any or all of these factors could overcome the relatively slight gravity dependent changes.²

The observation that a rise in PO_2 with tilting was not found in two term infants with normal lungs

while being mechanically ventilated could be due to positive pressure ventilation overcoming the effects of gravity on functional residual volume.

In conclusion, head up tilting increases PO_2 in healthy term and preterm infants, but it does not benefit infants ventilated for respiratory distress syndrome.

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Special report

The work of the Child Accident Prevention Trust

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In 1983 an article was published in this Journal describing the work of the Child Accident Prevention Trust.¹ Since that time many developments have taken place in the field of child accident prevention. There has been an increased recognition of the role of accidents and injuries in child health and the importance of accident prevention at an international, national, and local level. This has, in part, been a result of work undertaken by the Child Accident Prevention Trust. Much remains to be done, however, and doctors and other health workers involved with children must recognise the part that they can play in reducing this epidemic. Mortality and morbidity from accidents is the largest single problem in the health of children after the first year of life. The aim of this article is to stimulate interest in the problem of accidents in childhood especially among community paediatricians and clinical medical officers. Hospital doctors and general practitioners also have a particular part to play in drawing the attention of appropriate authorities to factors which have led to accidents that may have been preventable (see Annotation in this issue).

The work of the Trust can be divided into four main areas:

- (1) Hosting seminars and scientific meetings to encourage a multidisciplinary approach to the problem of accidents in children.
- (2) The establishment of expert working parties to review and make recommendations on particular accident problems.
- (3) The publication of guidelines on a variety of aspects of accident prevention, for use by professional groups and the general public.
- (4) Liaising with international, national, and local organisations concerned with accidents in childhood.

Meetings and seminars

The Trust aims to offer professionals from a variety of disciplines the opportunity to explore and appreciate their role in child accident prevention. Examples of such meetings held include:

- (i) A seminar organised jointly with the Consumer's Association and the Ergonomics Society to explore the role of the British Standards Institution, and its

contribution to child safety.² Speakers included Mr Alex Fletcher, the then Minister of State for Corporate and Consumer Affairs. (ii) A symposium for the medical profession opened by Sir Donald Acheson to provide a forum for doctors to present the results of recent research in child accident prevention.³ (iii) A guest lecture by Professor John H Pearn of the Department of Child Health in Brisbane on various aspects of accident prevention activities in Australia.

Expert working parties

The establishment of working parties enables the Trust to call upon the expertise of a variety of individuals and organisations whose work impinges on child safety with a view to approaching a problem from a multidisciplinary point of view. The Trust has found that this approach is particularly successful for a variety of reasons. Firstly, accidents in childhood are usually the result of factors that are the responsibility of more than one authority; therefore potential methods for prevention may come within the remit of several different professional groups. Secondly, an undertaking by all those whose activities impinge either directly or indirectly on the

safety of children may achieve a more sympathetic climate in which methods for prevention can be implemented. Thirdly, professionals from a variety of disciplines can ensure a fresh approach to a problem.

A working party was convened in 1983 to consider the problem of burn and scald accidents to children. Members included representatives from the Home Office, Department of Trade and Industry, Chief and Assistant Chief Fire Officers Association, as well as an architect, health education officer, and burns specialist. A fully detailed report⁴ and shorter version⁵ have been published; these contain many specific recommendations. These recommendations and the findings of the working party were launched at a seminar at which over 150 safety and health professionals, designers, fire officers, burn specialists, and government officials attended. The Trust is now pursuing the implementation of the recommendations with the appropriate authorities and government departments.

Initial work at the Trust seemed to suggest that the health visitor has a unique part to play in the prevention of childhood accidents. A working party was established by the Trust to explore this role in more depth. Through the working party a two year research programme funded by the then Health Education Council was undertaken with the support of the Health Visitors Association. This research has now been completed⁶ and evidence from this is being used as the basis for health visitor training programmes in child accident prevention.

The Trust's working party on children in cars has been reconvened as a result of recent changes in legislation and design in this area. As part of its work, the working party has undertaken a review of loan schemes for infant car restraints and is providing guidelines for authorities, groups, and individuals wishing to establish schemes. The working party will be producing a report within the next few months, which will include recommendations concerning future legislation in this area.

Guidelines for professionals

After the award to the Trust of the Consumer's Association Silver Jubilee prize in 1985 the Trust produced a booklet aimed at health visitors and mothers setting out the types of safety equipment currently available on the market.⁷ The booklet aimed to provide them with independent advice on the range and type of safety equipment available for children under the age of 5 years. An indication of the equipments' suitability and effectiveness was also given. The booklets were distributed through

local health education units and are currently being reprinted.

Work at the Trust had suggested that some quarter of a million children each year are treated in hospital as a result of an accident caused by factors related to the design of houses. It seemed that many of these accidents were directly linked to bad or inappropriate architectural design, and that very simple design changes could eliminate many of these. Research was undertaken to establish what particular features in the house were causing the major accidents and injuries, and what changes could be made by architects, designers, and house-builders to reduce the problem. The result was a set of guidelines published by the Trust aimed at architects, designers, and commissioning agencies suggesting simple and inexpensive design changes that could be made in new and rehabilitated housing to avoid such accidents reoccurring.⁸ These guidelines have now been widely distributed with the help of the National House Building Council and the Department of the Environment and have been very well received.

Research

The Trust undertakes research for a variety of organisations and government departments, in particular, the Department of Trade and Industry (DTI). Much of the research is in response to accident problems brought to the Trust's attention by government departments, health and medical professionals, and a variety of other organisations.

Several cases of suspected child abuse brought forward allegations that brain damage was caused by the over-violent oscillation of the babies in bouncing cradles. The DTI commissioned the Trust to undertake research to ascertain the forces and accelerations that might be produced through the use of bouncing cradles. The work was undertaken for the Trust by Dr PF Millington of the Department of Bioengineering at the University of Strathclyde.⁹ This research showed that the forces and accelerations associated with the use of bouncing cradles were extremely unlikely to produce brain damage. These results have been particularly important in terms of their medicolegal implications.

After the death of a number of schoolchildren because of the impaction of inhaled pen caps below the larynx research was undertaken, at the request of the DTI, on behalf of the Trust by Mr DB Mathias, ear, nose, and throat surgeon at the Royal Victoria Infirmary, Newcastle upon Tyne in association with the Newcastle University Department of Mechanical Engineering. The research investigated the cross sectional area of an airway that would

allow sufficient flow of air through it to keep a child alive.¹⁰ The results have seen the development by a number of leading pen manufacturers of a safer pen top that will allow a child to breathe even if inhaled.

The European Commission is currently supporting the Trust in the establishment of an ergonomics data bank of information relating to children. This work, being undertaken at Nottingham University, will bring together known information and data on detailed aspects of the physical size, weight, performance, development, perception, and behaviour of children of different ages. Such a comprehensive collection will be of use to manufacturers and designers of children's goods and safety equipment.

Inquiries and information service

The Trust's Resource Centre located in its London office offers a comprehensive library and information service on all aspects of children's accidents and their prevention. This service is aimed principally at professionals and researchers in the field, and it is widely used by the media and government departments.

Contacts with other organisations

The Trust's role as an independent scientific advisory body necessitates close cooperation with a number of other organisations concerned with children's safety. In particular, the Trust works closely with the British Standards Institution and the Health Education Authority. Many common areas of concern are shared with the Royal Society for the Prevention of Accidents (RoSPA), and the Trust continues to work closely with that organisation.

In order to encourage the establishment of local child accident prevention groups, a two day workshop was held recently on Policy Development in

child accident prevention, to which some 40 organisations sent representatives. Internationally, the Trust has developed close contacts with the European Economic Commission, the World Health Organisation, the International Standards Organisation, and the European Consumers Product Safety Association, as well as with organisations and colleagues in Australia, New Zealand, Canada, and the United States. It has recently been nominated as the United Kingdom representative in a joint examination of the problem with the Soviet Union, and in April it was a cohost with Swedish colleagues of an international meeting in Stockholm.

It is hoped that these various activities illustrate the strength and vigour of this growing organisation.

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Regular review

Clinical applications of nuclear medicine

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The use of nuclear medicine in paediatrics has experienced a rapid and continuous development over the past 15 years, despite the introduction of computed tomography, echography, and magnetic resonance.

Nuclear medicine is based on the principle that a radioisotope is an unstable substance that gives off energy at a particular level as it decays into a stable compound. The ability to 'label' certain radioisotopes allows a minute quantity of this isotope to be specifically directed at one cell type or organ so that functional images result.

This specific uptake may compensate the lack of resolution compared with other imaging techniques. For instance, the selective uptake of technetium ^{99m}Tc labelled dimercaptosuccinic acid (DMSA) by the tubular cells allows the recognition of focal areas of pyelonephritis, which can be missed by ultrasound or intravenous urography. Iodine 123 (^{123}I) labelled metaiodobenzylguanidine (MIBG) is selectively taken up by the chromaffin tissue, allowing the detection of neuroblastoma metastases, which are not seen by other techniques. Beside the morphological aspects the selective uptake or excretion, or both, of a tracer by an organ makes it possible to quantify one or more functions related to this organ. Nuclear medicine procedures are safe, minimally invasive, and generally expose the child to a very low radiation dose.

Patient preparation

Most radioisotope examinations do not require any patient preparation. In dynamic renal scintigraphy a well hydrated child is not only a happy cooperative child but hydration also permits optimum analysis of the renal scan. When searching for the presence of ectopic gastric mucosa the child must have nothing orally for 4 hours before the examination.

Sedation is rarely used in most paediatric institutions and also in those adult centres geared to carry out a considerable number of studies in children.

The general principle that radiation has to be kept at the lowest possible level has meant that those isotopes commonly used have a short half life (for example, ^{99m}Tc =6 hours or ^{123}I =13.3 hours) and

Radioactive tracers

The general principle that radiation has to be kept at the lowest possible level has meant that those isotopes commonly used have a short half life (for example, ^{99m}Tc =6 hours or ^{123}I =13.3 hours) and emit gamma rays at an appropriate level for a gamma camera. The ability to label ^{99m}Tc with various different specific non-toxic chemicals has allowed most examinations requiring nuclear medicine in paediatrics to concentrate on investigating various aspects of renal function, pulmonary perfusion, and disorders of the skeleton as well as the reticuloendothelial system. In addition, imaging of the gut and thyroid gland as well as congenital heart disease have all benefited from the use of ^{99m}Tc . Labelling of white blood cells with a ^{99m}Tc complex is also now available.

Radiation

'As compared to ionizing radiation used externally in diagnostic radiology, the use of radiopharmaceuticals results in internally absorbed doses delivered at much lower dose-rates, which generally are considered to have less biological effect.' This quotation is from the radiation protection body of the United States (National Council on Radiation Protection and Measurements, N°73,1983) and should encourage the use of nuclear medicine in paediatrics.

Low irradiation, no sedation of the patient, and absence of appreciable side effects characterise the radionuclide techniques, which provide useful morphological and functional information and are particularly well adapted to the paediatric patient.

Table 1 Tracers used in renal and urinary tract disorders

Tracers	Physiology	Indications
Diethylene triamine penta-acetic acid—technetium ^{99m}	Eliminated only by glomerular fraction	1,2,3,4,6
Hippuran ^{123} I	Eliminated by tubular secretion (80%) and glomerular filtration (20%)	1,4
Edetic acid—chromium 51	Eliminated only by glomerular filtration—not suitable for in vivo measurements	3
Dimercaptosuccinic acid—technetium ^{99m}	Uptake by the tubular cells	4,5,6
Perchnetate technetium ^{99m}	Tracer for bladder filling and voiding	2

Clinical indications

RENAL AND URINARY TRACT DISORDERS (TABLE 1)

Indications¹⁻¹³

(1) A differential diagnosis can be made between urinary obstruction and atonic dilatation from the renogram obtained with ^{99m} Tc labelled with diethylene triamine penta-acetic acid (DTPA) or ^{123} I Hippuran; parameters of whole kidney and cortical transit can be derived as well as response to frusemide.¹⁻³

(2) Diagnosis and follow up of vesicoureteric reflux, using either ^{99m} Tc perchnetate for the direct cystogram, or ^{99m} Tc DTPA for the indirect cystogram; both give a much lower gonadal irradiation than the radiological cystogram.^{4,6}

(3) When overall clearance has to be assessed instead of undertaking a creatinine clearance an accurate glomerular filtration rate may be obtained using two or three blood samples 2–4 hours after an intravenous injection of ^{99m} Tc DTPA or chromium-51 edetic acid (^{51} Cr EDTA). This latter technique is more accurate and easier to perform, it does not require urine collection and is useful in those diseases affecting the kidneys symmetrically.⁷

(4) Quantitation of individual kidney function. This is generally obtained from the early phase of a ^{99m} Tc DTPA or a ^{123} I Hippuran renogram, or from the ^{99m} Tc DMSA uptake. This is indicated in the preoperative and postoperative evaluation of uropathies and certain nephropathies, which may affect the kidneys asymmetrically.^{8,9}

(5) Precise topographical definition of parenchymal damage (acute and chronic pyelonephritis, trauma), kidney site, and morphology (pelvic kidney, transplant, horseshoe) using ^{99m} Tc DMSA static images.^{10,12}

(6) Aetiology of hypertension. Detection of the pyelonephritic scars of vesicoureteric reflux, using ^{99m} Tc DMSA (fig 1).¹⁰⁻¹² Detection of renovascular hypertension by combining a ^{99m} Tc DTPA renogram with the pharmacodynamic effect of captopril.¹³

Fig 1 shows a 5 year old boy who presented in mild chronic renal failure with polyuria and polydipsia. There was a history of recurrent urinary infections that had not been investigated. The intravenous urogram (not shown) failed to show a right kidney and demonstrated a poorly functioning left kidney with abnormal calyces. This ^{99m} Tc DMSA scan shows a high background activity. The left kidney is functioning better than the right (R) and focal defects are noted in the lower pole of the left kidney. The right kidney is seen to contribute 31% to overall function despite not being seen on the urogram. Comment: This child was found to be suffering from reflux nephropathy and shows the sensitivity of the DMSA scan in identifying func-

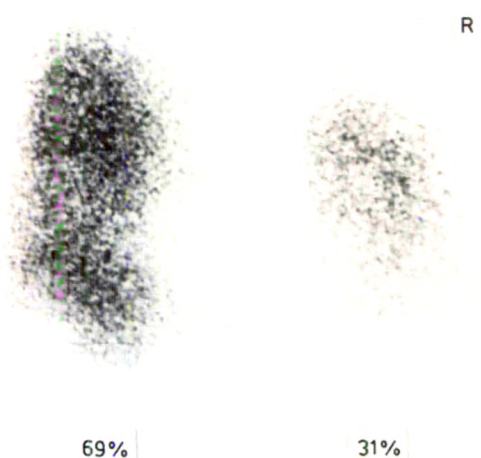


Fig 1

Table 2 Tracers used in pulmonary diseases

Tracers	Physiology	Comments	Indications
Macroaggregates—technetium 99m or human albumin microspheres—technetium 99m Krypton gas 81m	Regional perfusion	High quality static images, can be done at all ages, cheap and easy	1,2,3,4,5,6
	Regional ventilation	High quality static images during normal breathing through a mask, low sensitivity below 1 year of age for subsegmental defects, expensive, requires high organisation	
Xenon gas 133	Regional ventilation	Low quality static images after single breathing, needs patient's cooperation (patients must be older than 6 years), inexpensive	1,2,3,4,5,6
Millimicrospheres aerosols—technetium 99m	Regional ventilation	Still requires extensive standardisation	1,2,3,4,5,6 6

tioning renal parenchyma and focal defects within the kidney.

PULMONARY DISEASES (TABLE 2)

Indications¹⁴⁻¹⁸

- (1) To confirm or exclude the diagnosis of regional lung disease in the presence of normal or equivocal films from chest x rays (foreign body, bronchiectasis, aspiration pneumonia, small lung, hyperlucent lung). Furthermore, to select patients who should undergo more invasive investigations (bronchoscopy, bronchography) (fig 2). For instance, the probability of having bronchiectasis or a foreign body is very low in the presence of a normal scan.
- (2) To evaluate function in the rest of the lungs before surgical removal of a lobe (bronchiectasis, sequestration).
- (3) To detect intrapulmonary shunts and other vascular anomalies before angiography is performed (a negative result on scintigraphy could avoid angiography).
- (4) To follow up severe disease, like cystic fibrosis, or bronchiectasis, or sequelae of viral pneumonia.
- (5) To detect pulmonary embolism or primary artery disease—this needs combined ventilation and perfusion studies.
- (6) To evaluate mucociliary clearance.

As most ventilatory disturbances will necessarily and instantaneously be followed by a corresponding perfusion abnormality (adaptation mechanism), most ventilatory diseases (foreign body, cystic fibrosis, etc) can be investigated by either a perfusion or a ventilation scan. On the contrary, vascular disease (embolus, pulmonary artery disease) shows an abnormal perfusion and a relatively normal ventilation scan (mismatching). With a sequestered

segment, the perfusion scan is always abnormal, the ventilation scan may either show a matched defect or may be relatively normal.

Fig 2 shows a 6 year old girl with recurrent moist cough and wheezing episodes. The suspected clinical diagnosis was that of bronchiectasis. (a) The chest radiograph picture shows overinflation of both lung fields as well as the mediastinum displaced to the right with loss of the right heart border. The vessels in the right lung are also diminished compared with that on the left. (b) This shows the ^{99m}Tc macroaggregates perfusion scan. (c) This shows the Krypton—81m ventilation lung scan. These images were obtained in the right posterior oblique (RPO) projection and show a pronounced decreased activity of both isotopes throughout the right lung with total absence of activity in both the upper and lower zones. The left lung shows a segmental defect of both ventilation (V) and perfusion (Q) in the upper zone with a generalised decrease of both isotopes in the left lower zone. (R indicates the right side.) Comment: Further investigation confirmed collapse with bronchiectasis in the right lower lobe which was non-functioning on lung scan. The compensatory overinflation of the right upper lobe as well as the left lung have non-perfused and non-ventilated segments. This child was found to be immunologically abnormal and asthmatic.

HEPATOSPLENIC DISORDERS (TABLE 3)

Indications¹⁹

- (1) Jaundice—to exclude biliary atresia in the infant; to assess postsurgical patency of biliary tree; to assess drainage in choledocal cyst and the presence of dilated ducts—for example, Caroli's disease.
- (2) Detection and follow up of space occupying lesions in the liver in combination

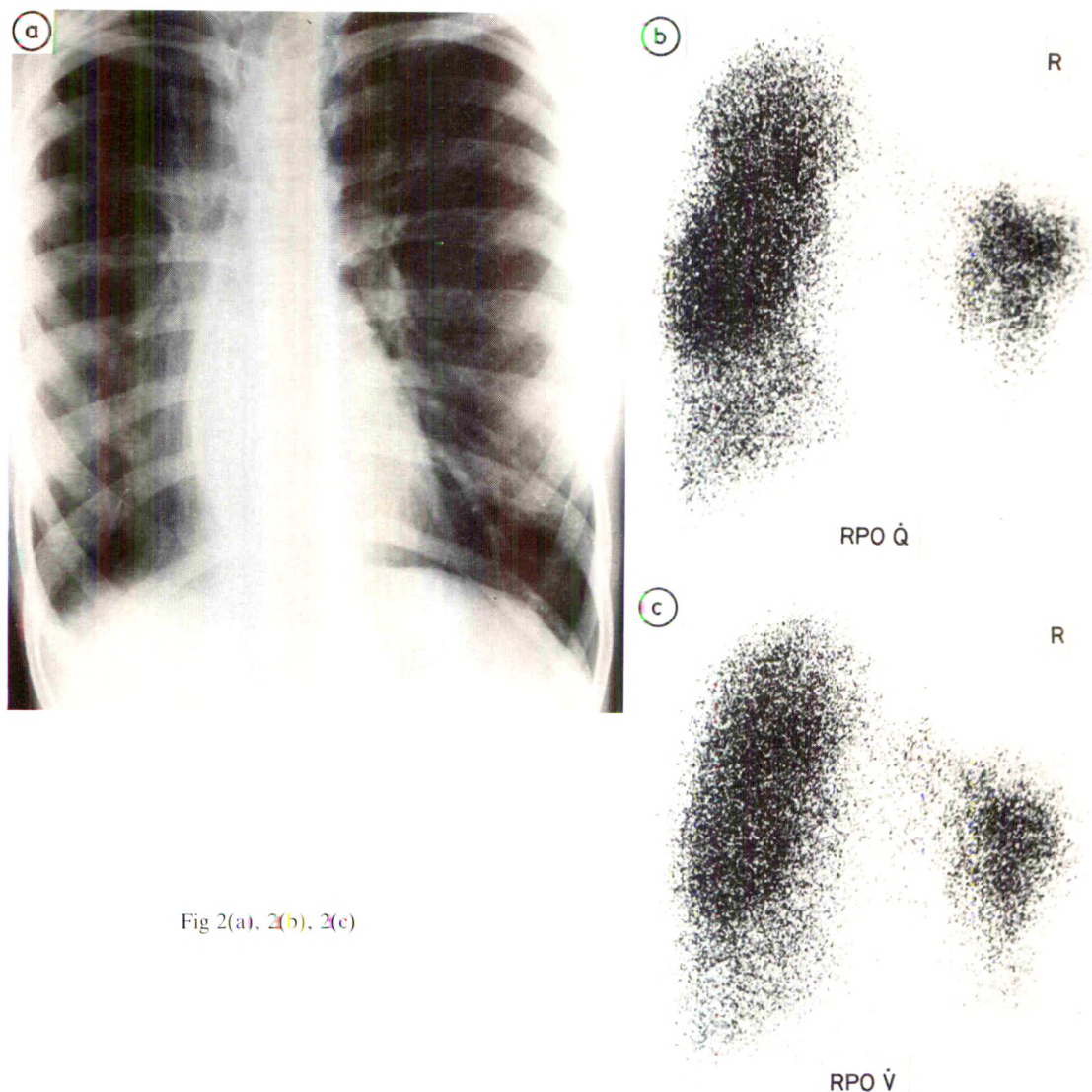


Fig 2(a), 2(b), 2(c)

with other techniques (ultrasound, computed tomography).

(3) To detect congenital splenic abnormalities associated with congenital heart disease (asplenia, polysplenia).

(4) To detect splenic trauma, or accessory spleen (idiopathic thrombocytopenic purpura).

GASTROINTESTINAL TRACT DISORDERS (TABLE 4)

Indications²⁰⁻²⁴

(1) Diagnosis and follow up of gastro-

oesophageal reflux (chronic vomiting, recurrent lung infections, near-miss sudden infant death syndrome, etc).²⁰

(2) Study of the oesophageal transit (caustic stricture, peptic oesophagitis, achalasia, neurogenic impairment of the peristalsis, etc).²¹⁻²²

(3) Diagnosis of a Meckel's diverticulum containing gastric mucosa.²³

(4) Evaluation of the gastric emptying time.²⁴

If the diagnosis of ectopic gastric mucosa is made the

perchnetate scan should not be performed during active bleeding as there is the possibility of a false negative result due to dilution or washout of the radioactivity. Premedications such as pentagastrin or cimetidine have been suggested to increase the sensitivity of the perchnetate scan. False negative results have been described (sensitivity ~75%); and positive abdominal images have been described in conditions other than Meckel but can generally be differentiated.

SKELETAL DISEASES (TABLE 5)

Indications^{19 25-27}

- (1) To detect primary or metastatic bone malignancies (fig 3).
- (2) To confirm the presence of suspected inflammatory or infective bone lesions with normal or equivocal x ray (osteomyelitis).
- (3) To diagnose avascular necrosis and to follow up revascularisation.
- (4) To diagnose and localise osteoid osteoma.
- (5) To diagnose bone marrow disorders (early diagnosis of metastatic disease and haematological disorders).
- (6) To investigate long term symptoms which

may be skeletal in origin—for example, a lump or backache

Normal ^{99m}Tc labelled methylene diphosphonate (MDP) bone scans have been reported in acute septic arthritis and also when osteomyelitis occurs in the young infant. Although uncommon, negative bone scans are seen in older children with osteomyelitis. White blood cells labelled with ¹¹¹Indium are used in some hospitals as a second or third choice investigation for suspected osteomyelitis especially in the newborn where the ^{99m}Tc MDP scan is unreliable in excluding the disease. Scans of white blood cells labelled with ^{99m}Tc hexamethyl propylene amine oxime (HMPAO) require evaluation in septic arthritis and in the young infant with osteomyelitis. ⁶⁷Gallium may also be used as a second choice isotope when the initial bone scan is negative or equivocal. A number of extraosseous abnormalities may concentrate ^{99m}Tc MDP; this is seen in neuroblastoma, splenic infarction in sickle-cell anaemia, myocardial infarction, soft tissues metastases of Ewing's sarcoma, ectopic calcifications, and in the intestine in necrotising enterocolitis.

Fig 3 shows a 2 year old child who was unwell and was found to be anaemic and hypertensive. The clinical diagnosis was neuroblastoma; this was

Table 3 Tracers used in hepatosplenic disorders

Tracers	Physiology	Indications
Colloid—technetium 99m	Uptake by the reticuloendothelial system of liver and spleen	2+4
Damaged red blood cells—technetium 99m	Selective uptake by the spleen	3,4
Iminodiacetic acid (N substituted)—technetium 99m	Early uptake by the parenchymal liver cell and excretion through the biliary ducts into the duodenum	1

Table 4 Tracers used in gastrointestinal tract disorders

Tracers	Physiology	Indications
Colloid—technetium 99m	Non-reabsorbed or modified in the stomach	1,2,4
Krypton 81 in glucose	Fast disappearance due to the ultra short life of the tracer	2
Perchnetate—technetium 99m	Actively taken up by the gastric mucosa	3

Table 5 Tracers used in skeletal diseases

Tracers	Physiology	Indications
Methylene diphosphonate—technetium 99m	Static image activity dependent upon blood flow and osteoblastic activity	1,2,3,4,6
Colloid—technetium 99m	Taken up by the reticuloendothelial cells of the bone marrow	5
Gallium 67	Non-specific uptake by inflammatory tissue	2
White blood cells—indium III Hexamethyl propylene amine oxime white blood cells—technetium 99m	Monitoring migratory pattern of the child's white blood cells	2

further suggested by high vanillylmandelic acid concentrations in the urine. (a) This shows the ^{99m}Tc methylene diphosphonate bone scan. This posterior view of the axial skeleton shows abnormal vertebrae with areas of both increased and decreased activity. Abnormal increased uptake of isotope is noted in the left femur. Uptake of isotope by the left adrenal tumour is also noted. (b) This shows the ^{123}I metaiodobenzylguanidine scan. The posterior view of the axial skeleton, pelvis, and femurs show

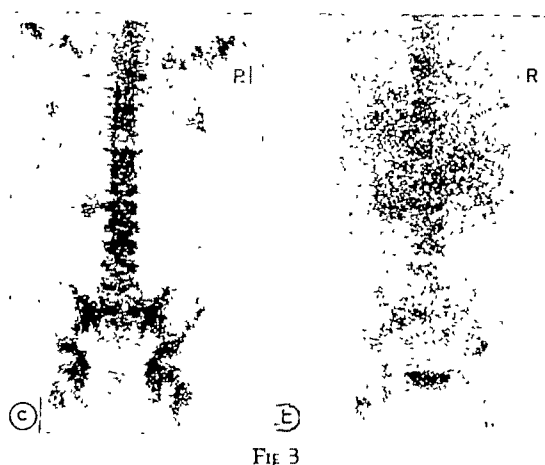


FIG 3

numerous bony areas taking up the isotope; this is abnormal. Isotope is seen in the left adrenal gland. Activity is also noted in the heart; this is normal. (R indicates the right side.)

THYROID DISORDERS (TABLE 6)

Indications²⁸

- (1) Definition of aplasia/ectopia or normally located gland
- (2) Evaluation of neck nodules and their relation with thyroidal tissues.
- (3) Diagnosis of nodular lesion in hyperthyroidism as possible hyperfunctioning adenoma (rare in children).

^{131}I Iodine is a well established tracer for assessing thyroid function. It is contraindicated in children because of the high radiation. The alternative tracers are either ^{123}I Iodine or ^{99m}Tc pertechnetate. There are protagonists of each isotope and in the investigation of a thyroid nodule it may be unimportant which tracer is used.

HEART DISEASES (TABLE 7)

Indications^{17 29-31}

- (1) Assessment of left to right heart shunt using ^{99m}Tc pertechnetate.
- (2) Assessment of right to left heart shunt using ^{99m}Tc macroaggregates (MAA).

Table 6 Tracers used in thyroid disorders

Tracers	Physiology	Indications
Pertechnetate—technetium ^{99m}	Selective uptake by the thyroid gland	1,2,3
Iodine 123	Selective uptake by the thyroid gland and incorporation in thyroid hormones	1,2,3

Table 7 Tracers used in heart diseases

Tracers	Physiology
Pertechnetate—technetium ^{99m}	This isotope will be taken via the right heart to the lungs then to the left heart and on to the systemic circulation. In the presence of a left to right shunt isotope will go from the left heart phase both to the systemic circulation and also back to the lungs. The shunt can be quantified.
Macroaggregates—technetium ^{99m}	The isotope will be trapped in the first capillary plexus and therefore after an intravenous injection all the isotope is normally stopped in the pulmonary capillary bed. In the presence of a right to left shunt the isotope is seen in the systemic circulation—for example, kidneys.
Red blood cells—technetium ^{99m}	As the isotope is attached to the red blood cell mass images of the pulsating heart can be obtained over a period of time in order that ventricular function can be assessed. Changes in function can be measured (ejection fraction).
Krypton gas— ^{81m}Kr	This isotope will come out of solution as soon as it is in contact with air. If the ^{81m}Kr is given by constant intravenous infusion then the isotope will enter the right heart and then the pulmonary circulation. The isotope will freely cross the alveolar membrane and be exhaled so that no isotope will reach the pulmonary veins or left heart normally. Good delineation of the right ventricular structures can therefore be reached, without any superposition of the left heart, this allows a measurement of the right ventricular contractility.

- (3) Assessment of left ventricular function using ^{99m}Tc pertechnetate (first pass) or red blood cells labelled with ^{99m}Tc (equilibrium).
- (4) Assessment of right ventricular function using ^{99m}Tc pertechnetate (first pass) or ^{81m}Kr infusion.

Recent progress in radioactive tracers

LABELLED WHITE BLOOD CELLS USING EITHER $^{111}\text{INDIUM}$ OR ^{99m}Tc HMPAO

Indications³²

- (1) To investigate when pus is suspected at any site (fig 4).
- (2) To investigate pyrexia of unknown origin
- (3) To investigate inflammatory bowel disease.

Tracers

White blood cells labelled with ^{99m}Tc HMPAO: the labelled white blood cells migrate to the focus of infection/inflammation where they accumulate. If the polymorphs are labelled then one may be able to distinguish active infection from inflammation.

White blood cells labelled with $^{111}\text{Indium}$: this is based on the same technique but gives a high radiation dose to the spleen and bone marrow. It is, however, still the isotope of choice for inflammatory bowel disease.

Fig 4 shows a ^{99m}Tc hexamethyl propylene amine

oxime scan. White blood cells labelled with the isotope were injected: the image at one hour is on the left, the middle image was taken at three hours, and the right hand image at 20 hours. The one hour image shows the spleen and liver with minimal lung activity persisting. The three hour image again shows the liver and spleen with a slight increase of activity in the mediastinum on the right hand side. The 20 hour image shows little activity persisting in the liver; the spleen is still clearly seen. The abnormal mediastinal activity is now quite pronounced. This was due to a mediastinal abscess in a child who had undergone a reoperation for oesophageal atresia and was feverish. (L indicates the left side.)

LABELLED METAIODOBENZYLGUANIDINE (MIBG) USING EITHER ^{131}I OR ^{123}I

Tracer

This tracer, a precursor of noradrenalin, is taken up by the adrenal medulla and also by neuroblastoma and pheochromocytoma even when these tumours are extra-adrenal in origin or spread.

Indications

Diagnosis of neuroblastoma (primary and metastasis) and pheochromocytoma (fig 3).³³

BRAIN BLOOD FLOW TRACERS

Tracers

^{123}I amphetamines and ^{99m}Tc HMPAO.

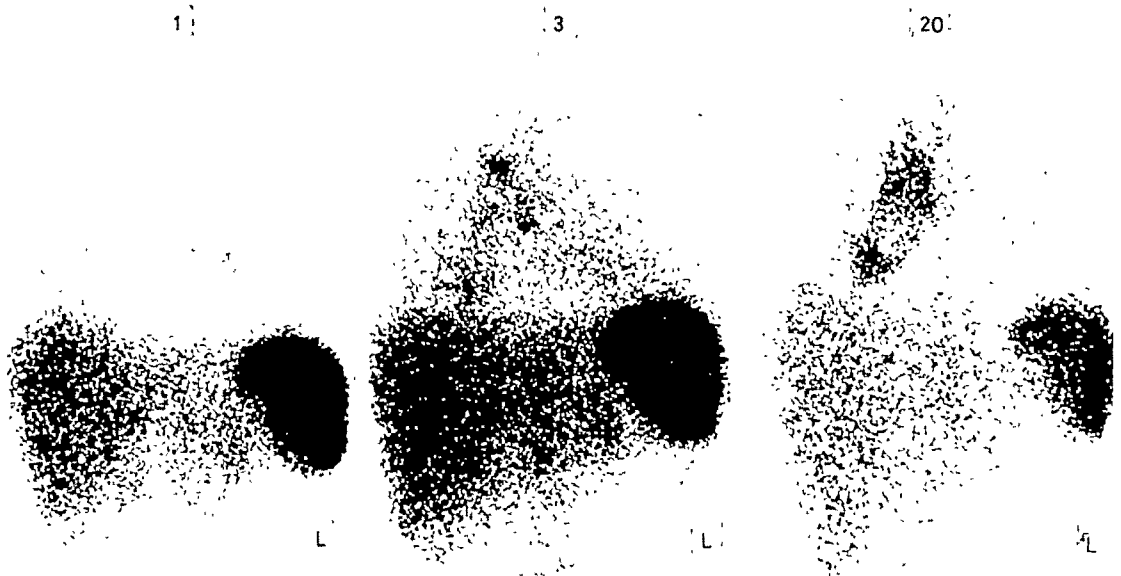


Fig 4

Physiology

Lipophilic tracers crossing the blood-brain barrier are giving an image of the blood flow.

Indications

Currently under review.

Conclusion

The role of radioisotopes in paediatrics is very specific in providing functional images of various organs. To gain maximum benefit for the patient the use of this technique should be in conjunction with other imaging methods. An abnormality on ^{99m}Tc MDP bone scan necessitates a high quality radiograph of the area; a ventilation/perfusion lung scan should always be accompanied by a chest radiograph. No renal isotope study should be performed without first carrying out an abdominal ultrasound examination.

When appropriately used, radioisotopes provide information that is important for patient care and frequently unavailable by any other technique.

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Current topic

A decade of insulin infusion pumps

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Over the past 10 years there have been many changes in the details of diabetic management. The development of home monitoring for capillary blood glucose and widespread availability of measurements of glycosylated haemoglobin have provided direct evidence that most diabetic children have poor or very poor glycaemic control. Additionally, there has been further evidence in support of the hypothesis that poor metabolic control predisposes susceptible diabetic patients to the microvascular and macrovascular complications of the disease.¹ Frustration that glycaemic control has not improved with regimens of one, two, or more recently, three² daily injections using the new, pure, and latterly, human insulins has focused attention on alternative ways of delivering insulin in the hope of achieving improved glycaemic control.

In 1978 continuous subcutaneous insulin infusion driven by a small battery powered portable pump was introduced as a research tool for improving glycaemic control in adults with insulin-dependent diabetes mellitus.³ The infusion system provided a continuous supply of unmodified short acting insulin throughout 24 hours with supplementary boluses of insulin initiated by the patient and given before meals. The developments coincided with the introduction of other 'tools' of management such as better education, the establishment of diabetic liaison health visitors, and an improved understanding of the role of diet and exercise in the management of diabetes.⁴ Portable insulin infusion pumps seemed to be a timely technological advance.

Early studies of the euglycaemic effects of infusion pumps were encouraging.^{5–8} Have the hopes engendered by these early favourable reports been fulfilled? Has the efficacy of insulin infusion systems under conditions of tightly controlled clinical trials in specialised centres been successfully translated into general clinical practice? Put more specifically

diabetes mellitus ranging from infancy, through school age, to adolescence, and young adulthood?

(2) How does insulin infusion compare in terms of blood glucose control with one, two, or multiple daily injection regimens?

(3) Are the indications for and complications of insulin infusion clearer?

(4) Does insulin infusion reduce the incidence of the microvascular and macrovascular complications of diabetes?

The effectiveness of long term insulin infusion

The documented world paediatric experience is small. The total number of children reported is less than 500 with no single centre reporting experience of more than 42 children.⁹ Many reports concern highly selected and motivated children and report favourably. Reports when children are selected for other variables, such as poor metabolic control,^{6–10} tend to have poorer results with higher withdrawal rates and often little advantage in glycaemic control for infusion pump users.

(A) YOUNG ADULTS

There has been one major report of longer term experience with insulin infusion pumps in young adults: Knight reported the experience of 45 young adult diabetic patients aged from 16 to 19 years of age who were approached about the use of infusion pumps as part of the Sheffield pump feasibility project.¹¹ Thirteen (29%) young people initially chose to try the treatment but only four of the 11 who actually started infusion pump treatment continued for one year; this represents a 64% discontinuation rate. These data compare with a 30% discontinuation rate among adult diabetic patients in the same clinic. Moreover, there was a relatively high rate of ketoacidosis and other medical complications in this group of young diabetic patients.

(1) Is insulin infusion an effective regimen that can be applied to large numbers of unselected children with insulin-dependent

(B) ADOLESCENTS

Since the early reports of insulin infusion in selected groups of diabetic children, there have been no large feasibility studies from the United Kingdom. Reports from the United States^{10,12} and The Netherlands¹³ support the general conclusion that infusion pump systems can work on selected adolescents but that there is a variable and usually high, discontinuation rate. The impression from recent studies is that overall, even among those who adhere to the pump regimens, there is only a modest improvement in glycaemic control. None the less within each population studied there was a small group of patients who could do well and for whom the pump was an acceptable advance in management.

(C) INFANTS

One report showed that infusion pumps can be used in the 12 month to 2 year age group.¹⁴ The pump is worn in a harness on the back, and may in selected cases provide an improvement in glycaemic control for these patients who present difficult management problems.

One recent study from The Netherlands is worth noting.¹³ Thirty four consecutive children, aged from 1.9 to 16.8 years, were randomised at diagnosis to treatment with an infusion pump or to one or two daily insulin injections. There were five withdrawals from treatment with the pump: four before the start and one after 28 months. After one year the mean (SD) glycosylated haemoglobin concentration in the group treated by infusion pump (9.5 (1.9)%) was considerably better than the conventionally treated group (11.3 (1.6)%) but still above the normal non-diabetic range.

Taken together (perhaps with the exception of the report from The Netherlands), these studies, on small numbers of young people, compare unfavourably with the large multicentre studies of adult diabetic patients where glycaemic control has been shown to improve and be sustained in the group randomised to pump compared with conventional insulin treatment for two years or more.^{15,16}

Infusion pumps have not been taken up enthusiastically by British paediatricians. The high discontinuation rate, modest improvement in glycaemic control, and lack of the necessary practical pump experience has meant that most paediatricians do not use infusion pumps. Many clinics have no children using pumps and our impression is that recruitment of new pump users in paediatric clinics has virtually ceased.

It is difficult to predict which patients will successfully use infusion pumps. Success does not seem related to intelligence, knowledge of diabetes,

parental interest, or social background.¹⁷ It is likely that patients who view the pump as a 'cure' for their diabetes will do particularly badly. The development of scales to measure 'adaptation to diabetes' may go some way towards providing an instrument to identify children who will do well on one or other particular regimen.

Comparison with intensified insulin regimens

In the early 1980s there was a series of reports comparing insulin infusion with intensified, three or four times a day, injection regimens. The report of Schiffrin *et al* provided the most information on the largest group of children, and it showed an improvement in glycaemic control for both intensified insulin regimen and insulin infusion.⁸ In her study the insulin pump provided better glycaemic control. The intensified insulin regimen was administered using conventional syringes and needles.

More recently the development of portable injection devices such as the Penject (Beckton-Dickinson Ltd), NovoPen (Novo Laboratories PLC), and Insuject (Nordisk UK Ltd) has meant that multiple daily injection regimens are easier to administer. There has as yet been no properly organised, prospective, and randomised, large scale comparison of an intensive portable injection insulin regimen compared with an infusion pump regimen. Such a study would be a difficult and expensive undertaking. It would have to address the decision to use pumps or pens as a contest between alternative regimens. Motivated and compliant patients, however, will probably improve on either regimen and the challenge lies in identifying which patients will do best on which regimen.

Indications and complications of insulin infusion

There are no absolute indications for insulin pump use in either adult or paediatric practice. Certain patients want to use infusion pumps because of their apparent convenience and potential flexibility: allowing them to alter or omit meals or snacks and to exercise at will. Children and parents may be seduced by the novelty and technology of the infusion system and believe that the pump will easily achieve improved control.

After a decade of experience it is recognised that there is an increased incidence of diabetic keto-acidosis in infusion pump users. This particular risk, however, seems to lessen as the clinic becomes more used to using pumps and patient education improves.^{18,19} It is now clear that children should test their urine for ketones when the stability of glycaemic control is stressed—for example, during infections.

Hypoglycaemia is probably no more common among pump users than in children on conventional insulin treatment, but information on which to assess this risk with any precision is not available. Mild hypoglycaemia, with a blood glucose concentration in the order of 3.2 mmol/l, causes variable symptoms, particularly a delay of reaction time, in diabetic patients.²⁰ The nature of the insulin pump system means that unless the subject senses hypoglycaemia the insulin continues to be infused—a situation that then becomes frankly dangerous.

Cognitive unawareness is traditionally thought to occur in patients with a long duration of disease. It has been reported, however, in those who have had diabetes for only five years and who have otherwise normal selected cardiovascular tests of autonomic function.²⁰ The dangers of hypoglycaemia may be potentiated by improved glycaemic control, which has been shown to reduce the plasma glucose threshold at which glucose counter-regulatory hormones are released thus theoretically reducing the level at which hypoglycaemic awareness is detected by the patient.²¹

Infusion site infection is uncommon but needs to be guarded against by frequent (say twice weekly) changes of infusion catheter and site. Some 10% of children have developed recurrent small subcutaneous abscesses that are unsightly and potentially life threatening. One death has been reported in an adult patient from endocarditis after such an infection.²²

Pump size and performance have been given as objections to the continuation with insulin infusion treatment. The pump may become physically or psychologically unsightly. System failure is common. Insulin aggregates in the cannula or needle or the cannula leaks. While the pumps themselves are mechanically reasonably reliable, patients may run out of supplies of insulin, cannulae, batteries, or blood glucose testing equipment.

Reduction of the complications of diabetes

Insulin infusion can improve glycaemic control but not all the metabolic abnormalities of diabetes are rectified.²³ The improvement in glycaemic control, however, has been sufficient to improve retinopathy, nephropathy, and neuropathy in adult patients.¹ In paediatric populations the modest improvement in glycaemic control has not proved adequate to reduce increased albumin excretion or reduce a raised creatinine clearance towards more normal levels.¹⁰ Thus the hope that improved glycaemic control would reduce the incidence of the complications of diabetes has not yet proved feasible for adolescent patients. Longitudinal studies are

urgently required to evaluate different insulin regimens against early markers of latent diabetic complications.

Conclusions

The advent of intensified insulin regimens over the past 10 years has coincided with other improvements in the management of patients with diabetes. These developments have drawn attention to the difficulties many diabetic adolescents face and have thus stimulated further exploration of insulin regimens, metabolic regulation, subtle physiological abnormalities, and psychological function. Intensive insulin regimens will expose deficiencies in the organisation of clinics and staff. Repair of these deficiencies is to the good of all patients but poses difficult questions about the use of resources. The infusion pump has in one sense been a false prophet and has not lived up to expectations in paediatric practice.

Insulin pens are being enthusiastically promoted and used in many clinics. The pens have a different but rational insulin delivery system and seem to be relatively safer than infusion pumps. There is, however, one preliminary report of rapid metabolic decompensation associated with pen use. (SM MacRury, AB Boal, KR Paterson. Diabetic ketoacidosis during NovoPen therapy. Poster 53. British Diabetic Association, Medical and Scientific Section Autumn Meeting, Cardiff, 1986). It is obvious that no insulin regimen is suitable for all users. The urgency remains to seek new strategies of management and to settle for nothing short of ultimate cure and prevention of diabetes. Insulin pumps have, however, clarified the reality of poor glycaemic control, the need for health education in diabetes, and the magnitude of the task ahead.

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Personal practice

Hospital teachers: medical interpreters or raffia mafia?

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Doctors as educators

Is it desirable that ward teachers, many of whom have been on the same ward for several years, should help out if the ward is short staffed by taking children's temperatures or monitoring their blood pressure? It is easy to imagine the outcry there would be if someone made that suggestion seriously. Arguments would speedily be mustered to show that these tasks, although not complex in themselves, are the proper professional concern of those who have been trained not only to perform the task but to understand medical theory. It is probable that no amount of counter arguments about the efficacy of 'on the job' training and the value of general experience in dealing with sick children would be deemed sufficient to persuade the medical profession to hand these procedures over to teachers, however capable and well motivated those teachers might be.

In contrast, every day in hospitals many doctors, some of them relatively young and inexperienced in communicating with children, attempt to explain to children, in a reassuring way, complex information about body malfunctions. They rarely have time to ascertain whether the child has the necessary grasp of how a well body functions that would enable them to understand the information they are trying to convey, and they may have only a vague notion of the way in which children's cognitive abilities develop. They may attempt to illustrate their exposition by a quick drawing on the back of an envelope or there may occasionally be a typewritten sheet explaining specific procedures given to parents.

On the whole it seems to be accepted that doctors should be expected not only to be able to perform certain medical procedures but should be equally able to explain these lucidly and at sufficient length, with diversions into teaching a basic biology syllabus

as necessary, to children of all ages and abilities. If they unaccountably fail in the latter task then parents, in an unfamiliar environment and handicapped by anxiety about their sick child, are expected to glean enough information to enable them to prepare adequately the child for whatever procedures are necessary. If teaching children really were so easy it would hardly be thought necessary for teachers to study for several years and to complete a probationary year before being deemed competent to undertake the task. Equally, if learning were so easy all children would remember everything they were told and we could say goodbye to all educational measuring devices from spelling tests to finals.

Childrens' encounters with hospital

Hospital teachers fortunately are not expected to miraculously acquire medical skills but it seems that many hospital doctors are forced to try to give themselves an in service course on teaching children. There may, however, be ways to develop interprofessional cooperation between doctors and hospital teachers that would make sense as a teaching strategy for most children who are in hospital for very short stays and which would also provide busy doctors with ready made educational materials to aid their communication with child patients and their families. This is not a problem confined to a few children. Statistics show that an encounter with a hospital is a normal part of childhood for many children. Unfortunately many children fail to gain all they might have done from the experience and at worst the encounter leaves the child with profoundly negative feelings about hospitals and doctors.

A quarter of the British child population will spend at least one night in a hospital before 7 years of age, and many more will visit accident and

emergency departments.^{1,2} Once admitted to hospital children (and their parents) will encounter many new and baffling experiences. It is certainly the case that apprehensions and fears are the frequent companions of illness, but for children in particular a stay in hospital is especially traumatic. Their concepts of illness and their interpretation of the meaning of medical procedures are emotionally laden. They have fears of abandonment and lack of control and young children often interpret the illness itself and the process of medical treatment as punishments for moral or social transgressions. They often have distorted ideas about their illnesses and suffer from disturbed fantasies involving mutilation and death, even about so called minor operations.

It is remarkably easy for health care professionals to forget how upsetting even the simplest aspects of hospital are for the layman. They fail to appreciate that for the patient a hospital admission is a special event fraught with anxiety. Confronted by strange faces, strange food, and a strange routine alone in a potentially threatening environment ignorance intensifies the feeling of being helpless in a hostile place. Even the simplest procedures in these circumstances become an ordeal. Really caring professionals would do well to remember that the patient's definition of a minor operation is one that is performed on somebody else. For a child the potential psychological trauma inherent in a hospital stay for even relatively minor surgery or treatment may be a high price to pay for improved physical functioning.

The medical profession has obviously been aware for a considerable length of time that hospitalisation and surgery can create a series of real or imagined threats for a child. The goal of ward management programmes is usually described as the restoration of physical function and mental well being while at the same time preventing residual psychological and somatic problems. In order to accomplish this doctors should regard psychological trauma accompanying surgery as a complication as deserving of their thought as post-operative bleeding or infection.

Avoidable stress

Tireless campaigning led to the recommendations contained in the Platt Report (1959) that the sick child's needs for his mother, for play, education, and as far as possible a normal routine, should be met in hospital.³ The pressure for a child and family centred philosophy of care has been maintained by groups such as the National Association for the Welfare of Children in Hospital (NAWCH). As a result, for many sick children one of the primary

causes of distress in earlier times, separation from their parents, is no longer an inevitable consequence of a hospital stay. Other equally avoidable stresses, however, still remain part of a stay in hospital for too many children.

The permutation of factors that affect the outcome of a child's stay in hospital, making it a constructive or a traumatic experience, are endless. Research has shown, however, that over and above the effects of the presence or absence of parents there remain other causes of emotional distress, many of which may be avoidable with adequate planning and resources. A simple example is the way in which the physical discomforts of pain and illness are further compounded by an unfamiliar institutional setting, while comfortable child oriented surroundings help to lower the child's anxiety and make him more amenable to examination and treatment. In addition, lack of understanding of illness, hospital routine, and medical procedures can all contribute to a child's emotional disturbance.

Appropriate psychological preparation for hospitalisation and surgery combined with supportive care can mitigate the stress experienced by patients. This has been an assumption underlying many clinical practices for several decades. There have been several studies that have concluded that children who are prepared for a stay in hospital and for hospital procedures display less emotional disturbance than those who were not. It has also been shown that it is more effective if this preparation can be given to both parents and children, particularly at what Vinstainer and Wolfer termed 'stress points'—for example, admission, blood tests, and the time before and after surgery.⁴⁻⁷

Unfortunately this takes a considerable amount of time. Busy medical and nursing staff may end up doing no more than paying lip service to this ideal, and with the increasing complexity and efficiency of modern medicine there is the danger that patients may be treated more and more as bits of machinery brought in for repair. Most doctors would strenuously deny that they did not communicate adequately with patients or their families but of all the criticisms levelled at doctors the most common concerns their failure to tell patients the things that they want or need to know. Fletcher and Robertson concluded that the difficulty parents have in getting enough authoritative information about the treatment, progress and aftercare of their children is a 'common and well-founded complaint.'^{8,9}

Barriers to effective communication

Even those doctors who do make valiant efforts to

convey information to patients or their families are likely to underestimate the problems arising from their lack of a simple common language with a shared meaning. They may not realise that patient's ideas about human anatomy may be quite bizarre and that knowledge of the simplest concepts of physiology may be totally lacking. Boyle found that there was not 100% agreement among doctors in one hospital on definitions for simple medical terms or in choosing the site of the heart on an anatomical diagram! Small wonder that he found that patients did not reach agreement on definition for any term. He suggested that clinical investigation had simply verified his impression that there are large areas of misunderstanding between conventional medical opinion and what he charmingly termed 'the vagaries of the lay mind.'¹⁰

Friedson has suggested that communications between doctors and patients break down because of the doctor's professional contempt for the patient's ability to enter into informed cooperation with his consultant.¹¹ It is proposed that this is the dominant professional's way of maintaining his prerogative to diagnose and forecast illness and that while he does not want anyone else to give information to the patient he shows a considerable disinclination to do so himself.

Even if one takes a less cynical view of the current system of hospital care, the odds appear to be stacked against effective communication between physicians on the one hand, and children and their families on the other. In modern hospitals communication problems are compounded by the fact that doctors and nurses see the children in their wards for very short periods of time. Pill found that the average amount of time the nursing staff in a hospital ward spent with each child was just 28 minutes, most of this time being used to perform routine tasks rather than fulfilling the child's emotional needs.¹² It is not then surprising that MacCarthy, in his study of communication between children and doctors, remarked 'It is a sad admission that on the whole paediatricians have very little relationship with children in the sense of a one-to-one confidential relationship.'¹³

Teachers as interpreters

There is usually someone in the children's ward, however, who may well have this sort of relationship with each child and who spends a considerable amount of time working with them and their families. The ward teacher is trained for several years in the art of communicating with children and is well used to breaking down all kinds of complex concepts into manageable bits of knowledge.

Teachers will never assume that just because children have been told something once, twice, or six times that they necessarily understand it. Well inured to classroom howlers they may be more ready than the most eminent paediatrician to deduce that a child may have construed 'oedema in the stomach' as 'a demon in the stomach' thereby suffering unnecessary terrors.

In a totally alien environment the teacher is the one professional who has a common frame of reference with the child and who belongs to the child's everyday well world. Unlike other adults they meet in the hospital, children can make a reasonable guess at the sort of demands this person will make on them and can be totally confident that at least here is one new found friend who—unless it is a sewing lesson—is unlikely to start advancing upon them with a needle!

Hugh Jolly pointed out that a child's hospital stay should be able to offer more than the prime aim of helping them to recover from an illness. He contends that it should be orientated so that the child learns as much as possible from the experience.¹⁴ His, and my, view of the ward teacher is not that of some anonymous ward fixture, trailing raffia and incomplete jigsaws, but rather someone who is a 'specialist exploiting the potential of the hospital environment'. Helping children to interpret and evaluate experience is not just a part of the hospital teacher's job, it is something all teachers do. In the threatening, unfamiliar hospital environment this aspect of the teacher's role assumes a particular importance.

The hospital teacher's role, however, could extend well beyond this and they could also offer a valuable service to the medical profession in providing written 'user friendly' materials that deal factually with basic physiology, hospital procedures, and routine. Before more conservative readers throw up their stethoscopes in horror may I say that we have already begun to do this in Newcastle with the active cooperation of several departments and the results to date have been very encouraging. We have developed worksheets that aim to use the unique hospital environment as a teaching opportunity. The format of the sheets vary but they include information, quizzes, and suggested activities that are aimed at children. The worksheets are printed and use photographs of hospital personnel and technology. As they are not obviously 'kids stuff' some of them are also acceptable to many adults. Although this spillover into adult education was envisaged at the outset, we had not expected that this would include a request from one director of nursing for copies of our sheet on 'How A Gamma Camera Works' for her nursing officers!

The sheets are produced in close consultation with the department or professional concerned. Drafts are sent back and forth between our service and the department or consultant involved until they are completely happy with the information they contain. In some cases the worksheets then go to that department and they control their distribution. The Hospital Teaching Service is merely acting as a 'translation service', helping to put across this information in a form children and their parents can readily comprehend.

Interprofessional collaboration

Despite the apparent benefits of someone transcribing in simple terms what a good physician would wish to convey to a child and their parents so that it is available for consultation at leisure, some persuasion has been necessary to allow us to offer this service. Our attempts to initiate this kind of cooperation are not always greeted with universal delight. Occasionally it is difficult to decide whether this stems from the medical profession's defence of the exclusivity of their 'high status knowledge' or genuine fears that information will raise rather than alleviate patient stress. As educationalists simply attempting to offer our specialised services to professionals with a different orientation it has sometimes appeared to the vagaries of this lay mind that in some branches of medicine three consultants gathered together provide at least five shades of opinion.

Some medical colleagues maintain that each doctor works in such an idiosyncratic way that it would be impossible to produce a worksheet everyone would be happy with. One would assume that the general layout of normal skeletal, digestive, or circulation systems can hardly be a matter of contention and in fact form part of general biology courses in schools so there can be no logical objection to teaching these in hospital at a time when they are of particular interest to the child. Those worksheets that use a particular physician's approach, which may in part differ from that of his colleagues equally present few real problems. We are quite happy to produce 'one off' versions for use in different wards while the distribution of highly specific information is in the hands of the departments concerned. It is hard therefore to see how this kind of collaboration in the production of teaching materials presents any threat to the doctor or patient. Although there may well be many areas of medicine where doctors may feel the service we are offering is inappropriate, there are surely many more where instantly available information prepared to each department's own specifications

would greatly ease the physician's difficulties in explaining to patients exactly where the offending organ is situated in the body, how it works normally, and what they intend to do to put it right.

It is elitist and illogical to try to maintain an illusion that medicine and surgery are some kind of esoteric mysteries and that the preparation of teaching materials could not be done by other professionals with more time and more expertise in the field of child communication provided they receive adequate information and guidance from medical personnel. Has it ever been suggested that science teachers should be qualified nuclear physicists before they are allowed to explain to children the principles of nuclear fission? While it is obviously important that it is the doctor who explains the abnormalities in functioning that have landed the child's body in hospital, it is not necessarily a doctor who can best explain to a confused and frightened child how normal body systems function, although they and their parents need this information in order to put into context what they are told by their doctor.

Although Vaughan was sure that 'a short while in a hospital ward cannot help but make one appreciate that much of what is said to children (and for that matter to parents also) is beyond their intellectual grasp, particularly if they are anxious and in strange surroundings',⁵ even the most aware paediatrician may forget that it is not enough for a child to be told a fact once or twice—it has to be assimilated. The blame for this lack of understanding does not lie entirely with doctors. Many studies have shown that after routine consultations the average patient remembers only half of what he has been told, and others record that even when special care was taken to provide full information as many as a third of the patients forgot what they were told and thought that they had never been told it.¹⁵

The role of parents

It is important to remember that it is not only the children who need to know what is going on. Research has shown that information given to parents is usually deficient in both quantity and quality even though in reality it is the parents who are generally addressed in any consultation with a child, even older children being 'routinely and smoothly excluded from the bulk of the action within most consultations'.¹⁶

It is essential for parents to have accurate information otherwise they will not be able to prepare their child adequately and the stress of their own ignorance may result in 'emotional contagion' from the worried parents further distressing the sick

child. Pious medical belief that parents will ask busy doctors about anything they do not understand contrasts with the parent's view that despite the air of 'deliberate jollity' on ward rounds it was so rare for doctors to volunteer information that parents felt it was 'somehow deviant or indecent to ask for it'.¹⁷ The root of this problem lies not in the nature of doctors or of patients but in the hurried conditions of hospital work. As this situation seems unlikely to improve in the foreseeable future it is even more essential that the medical professions take advantage of all aids to communication with patients that may be on offer.

There is a need to produce more materials and activity sheets for parents and children to work on together. These can reduce stress from potentially threatening events through the communication of accurate information about the event. Such material provides the child with a cognitive framework within which he can appraise the potentially frightening and disturbing events that will be experienced and will set the scene for an imaginative mental rehearsal in which 'the work of worrying' can take place.¹⁸ To truly understand something unknown and fearful a child needs opportunities to come back to it in his own time.

Ignorance is not bliss

Many, if not all, doctors used to believe that it was bad for patients to know too much about their illness but one thing is certain, if such information is withheld or given inadequately by doctors the child does not go through his hospital stay in a blissful ignorance. To an ill patient no news is not good news. It is an invitation to fear and the fears in fantasy far outweigh and are more terrifying than any reality-fears could ever be.¹⁹ If adults dismiss the idea that children in hospital are often anxious or sad and that these feelings can have far reaching effects, they may well be resorting to a kind of 'functional blindness' by which they spare themselves an acute awareness of children's mental suffering that they feel powerless to alleviate. In practical terms the child's negative feelings can transform themselves into anticipatory anxiety before actual medical procedures; this can result in a lack of compliance during treatment and lead to a protracted and difficult readjustment.

Properly designed preparation material used by parents with their children before medical procedures can considerably alleviate the effect that high anxiety on the part of the parent can have on the child's apprehensions. 'Prepared' children are clearly less anxious and more cooperative than 'unprepared' children. Even where there is apparent

agreement that children should be told what is going to happen in medical procedures, however, excuses are still made for not giving this information. Professionals cite lack of time as the reason, and parents and teachers feel they do not have adequate information to do the job properly. Meanwhile children continue to suffer needless fears and develop negative attitudes to hospitals, doctors, and health care.

Conclusion

Almost every situation has within it the potential for growth, and health care encounters are no different. They need not be purely traumatic but instead can be constructive learning experiences. If a child and his family are to gain maximum benefit from a stay in hospital it would seem that an important and easy way to help this would be for hospital teachers and medical and nursing staff to enter into active collaboration to ensure the patient has adequate information in an easily assimilated form. Although children may still find it difficult to welcome the prospect of a hospital admission, at least some of the unnecessary traumas will be removed and we will be closer to observing Florence Nightingale's dictum that 'The very first requirement of a hospital is that it should do the sick no harm.'

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Selective medical examinations on starting school

Sir,

We read with interest the paper by O'Callaghan and Colver.¹ We agree that school health services need evaluation. We disagree, however, with the inference that the sole function of the medical at school entry is to identify treatable physical problems.

The total child population must be examined at some stage. The Newcastle team are choosing to do this three times preschool. One is hardly surprised, therefore, at the low number of new problems identified at school entry. In Peterborough, full medical examination and development assessment preschool is largely reserved for those children screened out by the health visitor.

Seeing the total population preschool is notoriously incomplete, particularly in urban areas. We positively retain the school entry medical for this and the following reasons:

- (1) School 'fitness'—medical, educational, and social—is seen in the school setting.
- (2) Parents and children are introduced personally to the school doctor and nurse; this facilitates self-referral if problems arise later.
- (3) It is perceived as important by both teaching staff (National Association of Head Teachers. The NAHT view of the future requirement for school health service provision.) and by parents (99.6% consent to medical, 88% accompany their child, personal observation).
- (4) In this authority children enter school at the age of 4 years (an age often chosen for preschool medicals).

During the school year 1986-87, 2877 school entrants were medically examined in Peterborough. Altogether 1770 important problems were identified (that is, required action or follow up); 742 of these were discovered on screening vision and hearing—an activity few would dispute. Furthermore, 17.6% of the children had impor-

tant educational problems that were discussed with teaching staff. A proportion of the problems were known to parents and family doctors before the medical but appreciable numbers were not (table).

There have been tremendous changes in the nature of preventive child health care over the past 10 years. We are now far more involved with behaviour and adjustment problems and health education. We heartily endorse the comments on the importance of the school entry medical contained in the report *Investing in the Future*.² We recommend it as an economical use of doctor time.

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Sir,

The excellent paper by O'Callaghan and Colver on selective preschool medication examinations voices the misgivings many of us have about developmental screening or surveillance, in general.¹ Quite clearly the concept is too wide and unfocused to allow any useful information to be gathered, other than for epidemiological reasons.

My experiences with the six week developmental check are rather similar, over a two year period I examined 218 consecutive 6-8 week old babies in a community paediatric clinic. (This was part of a separate study, which was looking at acute infantile colic and its possible relationship to maternal psychiatric illnesses as measured by the General Health Questionnaire.)² From the purely medical point of view, however, developmental surveillance was a very disappointing business. I picked up nothing that I could refer to our local paediatrician as a new abnormality. Even worse, every abnormality I did discover was already known to the general practitioner or hospital clinic. A couple of mothers wanted to know 'if I was going to shake the rattle' or in some way test the development of their babies. A pass was expected and, even worse, was equated with being intelligent.

Had I not been looking specifically at the possible association between crying babies and maternal psychiatric problems, however, I would not have picked up a small number of medical reasons for these babies to cry (two urine infections, one case of otitis media) and a far larger number of mothers with psychiatric problems (46 women).

Table Proportion of problems unknown to mothers and general practitioners (total number of children=2877)

Problem	No (%) of children with problem	No (%) of mothers unaware of problem	No (%) of general practitioners unaware of problem
Physical	548 (19)	142 (26)	231 (42)
Speech and language	202 (7)	26 (13)	119 (59)
Neurodevelopmental	117 (4)	42 (36)	89 (76)
Behaviour	161 (6)	15 (9)	123 (76)

This led me to feel that the routine six week developmental physical examination, in its present form, is probably a waste of time.

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Trends in birth prevalence of cerebral palsy

We would like to add our comments to the correspondence arising from the recent publication of Prof. Pharoah and colleagues on trends in birth prevalence of cerebral palsy.¹

There has been an interesting swing in thinking on the origins of cerebral palsy over the past few years. This has arisen mainly from the observations derived from registers which have been compiled of children with cerebral palsy within geographically defined populations. It has become increasingly clear when surveying the problem from this community perspective that although low birthweight infants are at increased risk of cerebral palsy, many infants who later manifest signs of cerebral palsy had either a low birth weight nor a recognisable perinatal insult.

On the other hand there has been an increasing understanding of the associations between evolving neuro-pathological changes in the brain of the low birthweight infants, as detected by imaging techniques, and eventual clinical outcome.² This has led to the sort of claim made by Dr Barson that 'most infants with cerebral palsy have been admitted to a maternity hospital with a morphologically normal central nervous system whilst in utero and subsequently discharged to the community with pathological cavities in their brains.'³ This may be the perspective of those involved with immediate clinical care of low birthweight infants in a special care nursery but ignores the question of the aetiology of cerebral palsy in other babies.

Preliminary figures from the Oxford Region Child Development Project suggest a different view. This study has been establishing a register of infants with serious impairment, including cerebral palsy, born from 1984 onwards to mothers resident in the Oxford region at the time of delivery. Although the oldest infants on the register are now only 3½ years old, 58 infants from a total 1984 birth population of 31 311 have been diagnosed as having cerebral palsy. This gives a birth cohort prevalence rate of 1.82/1000 live births. Of the 570 infants with a birth weight of less than 2000 g, 17 have cerebral palsy. They represent only 29% of the 53 children with cerebral palsy.

We do not wish to minimise the risk of later motor impairment in the low birthweight population and the need

for continued monitoring of the outcome of the increasing numbers of extremely low birthweight survivors. At the same time we would support the view that the aetiological origins of most cases of cerebral palsy must be sought outside the immediate perinatal period.

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Members of the Steering Committee are
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R King, A J MacFarlane, J A MacFarlane,
A C Turnbull, and A Wilkinson

Carriage of penicillin resistant pneumococci

Sir,

While studying the pharyngeal colonisation by *Streptococcus pneumoniae* and the absence of penicillin resistance among pneumococci isolated from healthy Mexican children, we noticed the paper by Klugman et al that reported the relative penicillin resistance of *S pneumoniae* in 303 urban and 156 rural black children, this resistance was seen in 14% of urban carriers and 19% of rural carriers. The authors obtained those figures after screening isolated strains with methicillin discs and subjecting those organisms with halos of less than 25 mm in diameter to a quantitative antimicrobial test to confirm the resistance.²

The prevalence of such strains in South Africa may be even higher. Other investigators have shown that the methicillin discs can miss relatively resistant strains of *S pneumoniae* in 9% of cases, incorrectly identifying them as sensitive (that is with halos of greater than 25 mm in diameter).³ In addition, another paper by Klugman et al reported that when they were screening for resistance with methicillin discs they found 20% of falsely susceptible *S pneumoniae* strains, but they offered no explanation for this.

Consequently, if the limits of error given^{3 4} were used to calculate corrected figures, the results found¹ could be interpreted as showing resistant strains from 19% to 25% of the urban population and from 23% to 28% of the rural

population; the technical problem is that testing for antimicrobial susceptibility to obtain minimum inhibitory concentrations was only performed for strains resistant to methicillin by diffusion.¹

It may therefore prove more reliable to screen for penicillin resistant pneumococci using oxacillin discs that do not yield false sensitive results,³ so avoiding the risk of primary misclassification of clinical isolates responsible for invasive disease.

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Drs Klugman and Koornhof comment:

The recommendation for the use of oxacillin in preference to methicillin discs is based on the observation by Swenson *et al*¹ that three of 34 strains resistant to penicillin were falsely identified as susceptible using a 5 µg methicillin disc, compared with 0 of 34 using 1 µg oxacillin discs after incubation on Mueller-Hinton sheep blood agar plates in ambient air. Jacobs *et al*² showed that two of 29 compared with one of 29 were falsely identified as susceptible, using the two discs, respectively, after incubation on Mueller-Hinton agar with 5% lysed horse blood in ambient air. Neither of these differences is significant. Though a definitive answer to the advantages of one method over the other rests on an analysis of a larger number of strains, even a combination of the above data fails to show a significant difference between the tests, giving a false susceptibility rate of five of 63 (8%) with the methicillin disc compared with one of 63 (2%) with the oxacillin disc ($\chi^2=1.57$, $p>0.2$, with Yates' correction).

The 20% false susceptibility rate quoted by Dr Conde-Glez from another of our papers,³ is due to his misinterpretation of our presentation of all multiply resistant strains, identified in various day care centres, as multiply resistant penicillin susceptible (MRPS) strains. No inference of the prevalence of false susceptibility can be drawn from that study. A possible estimation of the true prevalence of penicillin resistance in urban and rural children may be calculated, assuming that for every 58 strains identified as resistant using the methicillin disc, a further five are missed. Using this estimation four additional strains to the 43 resistant strains were probably missed out of 206 isolates in the urban study, and three additional strains to the 30

resistant strains out of 96 in the rural study. We believe that the importance of these differences in carrier rates is unimportant.

We do agree, however, that primary misclassification of isolates responsible for clinical disease, especially meningitis, may be important in individual cases. The data of Jacobs *et al*² indicate that neither test is 100% sensitive. In areas with high prevalence of endemic resistant pneumococci we recommend that minimum inhibitory concentrations be determined on all pneumococcal isolates from cerebrospinal fluid. Finally the distribution between resistant and intermediately resistant strains cannot reliably be made with either of these disc tests¹ and must rely on MIC data from minimum inhibitory concentrations.

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Post-streptococcal glomerulonephritis in Hong Kong

Sir,

We were interested to read the recent report of Leung *et al* on post-streptococcal glomerulonephritis in Hong Kong.¹ It is now commonly assumed that this condition is rare in developed countries but our recent experience would lead us to think otherwise.

Since July 1985 we have documented a post-streptococcal aetiology in 11 of the 16 patients with acute glomerulonephritis referred to our unit. Nine of the 11 have been diagnosed since December 1986. We have recently reviewed the case notes of all 11 patients.

One obvious difference from the Hong Kong report is that macroscopic haematuria was the commonest presenting symptom in our series. It was present in eight out of 11 patients with only three having oedema as the main complaint. Group A β haemolytic streptococcus was isolated from the throat swabs of eight children, two of whom had received prior antibiotic treatment. In addition nine children had a raised anti-streptolysin O titre, seven a low serum C3 concentration, and seven raised C3 degradation products.

In general the nephritis was mild and no patients required acute dialysis. Four required drug treatment for hypertension. One of our patients presented with a dense right hemiplegia having had eight days of haematuria at home. We noticed that one child in the Hong Kong series presented with a convulsion due to hypertensive encephalopathy and this further illustrates the acute morbidity and occasional mortality associated with this illness.

We also assume that the recent increased prevalence of post-streptococcal glomerulonephritis may be due to an

increase in nephritogenic strains circulating in our community. There have been no recent case of rheumatic fever.

It is important that paediatricians should still consider the possibility of post-streptococcal glomerulonephritis. Children should be investigated in a thorough and consistent manner because as well as the acute problems an accurate diagnosis is essential for long term prognosis.²

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Sir,

We read the article by Leung *et al* with special interest because post-streptococcal glomerulonephritis is also the commonest glomerulopathy in our community.¹

In 1986, 57 children with acute post-streptococcal glomerulonephritis were referred to the Clinic for Children's Diseases in Skopje. (A Sajkovski, V Tasić, D Kuzmanovska. Acute post-streptococcal glomerulonephritis. Abstract presented at the Third Scientific Meeting of Yugoslav Nephrologists, Sarajevo, 1987: 75.) Two of them (3.5%) presented with hypertensive encephalopathy, nine (15.8%) with cardiovascular failure, and seven (12.3%) with uraemic syndrome.

In 1982 we saw 85 children with acute post-streptococcal glomerulonephritis, of these 25 (30.6%) had hypertensive encephalopathy. The analysis of factors associated with the high incidence of acute post-streptococcal glomerulonephritis in our community showed that most of the children lived in unhygienic and very bad social, economic, and educational conditions. Preceding streptococcal infections had not been adequately treated and the signs of acute nephritis were not recognised until late; hypertensive encephalopathy then followed. Pruritus and scabies impetiginosa are still important aetiological factors for acute post-streptococcal glomerulonephritis. Although there are a lot of differences between our communities, we think that acute post-streptococcal glomerulonephritis is still a 'social' disease and Leung's overcrowded living conditions need much more explanation.

Reference

- 1 Leung DTY, Tseng RYM, Go SH, French GL, Lam CWK. Post-streptococcal glomerulonephritis in Hong Kong. *Arch Dis Child* 1987;62:1075-6

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Increased main urinary metabolite of prostaglandin F_{2α} excretion in childhood migraine

Sir,

We read with interest the paper by Salfeld *et al* on the effects of dietary vasoactive amines in the aetiology of childhood migraine.¹ They found that dietary vasoactive amines did not influence childhood migraine.

We have not tried dietary manipulation but we measured plasma renin activity, plasma noradrenaline concentration, and 12 hour main urinary metabolite of prostaglandin F_{2α} (PGF-MUM) excretion in children with a history of migraine (n=43).² Children were divided into two groups: those with and those without headache at the time of investigation.

Urinary PGF-MUM excretion was significantly increased in children with headache (n=23) compared with those without headache (n=20) (1210 v 780 ng/12 hours, p<0.05); the plasma renin activity and noradrenaline concentration did not show any difference between the two groups.

These findings suggest that simultaneous study on both dietary manipulation and hormonal investigation especially on prostaglandins may be needed to clear the conflicting results on the role of vasoactive amines in the aetiology of childhood migraine.

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Book reviews

Surgical Treatment of the Epilepsies. Edited by J Engel Jr. Pp 746. \$150 hardback. Raven Press, 1987. ISBN 0-88167-002-2.

This is a comprehensive account, provided by international experts in the field, of present day understanding and practice of the various surgical approaches to the treatment of the epilepsies. The book is not only concerned with surgical procedures, along with excellent reviews of 'intractability', the natural histories and the clinical characteristics of the epilepsies concerned. There are discussions with extensive references of presurgical evaluation (including radiological investigations and neurophysiological assessment), extracranial and intracranial electroencephalographic recording and assessment of outcome from various points of view. Appendices are concerned with surgical techniques and surgical assessment protocols in different epilepsy surgery centres in North America and Europe, and with kindling. Many practical issues are covered including the indications for surgery. The overall place of epilepsy surgery in treatment might well be underestimated because of insufficient interest among neurosurgeons and a lack of familiarity with its potential role, perhaps especially in paediatrics. Important research topics are also identified including the relatively neglected areas of neuropsychological, psychiatric, and

social assessment before and after operation.

The book provides a very appropriate way of commemorating the publication in the *British Medical Journal* of 1886 of Victor Horsley's classic paper on brain surgery. It constitutes an excellent reference for all the disciplines involved in the surgical approach to the epilepsies.

G STORES

Sickle-Cell Anemia and Thalassemia: A Primer for Health Care Professionals. RG Huntsman. Pp 223. £5 (or \$10 US/Can) paperback. Canadian Sickle Cell Society, 1987. Available from: Canadian Sickle Cell Society, Sales-Despatch, PO Box 13156, Station A, St. John's, Newfoundland, A1B 4A4, Canada. ISBN 0-921037-00-7.

This book compresses an enormous range of clinical and scientific knowledge about the haemoglobinopathies into a compact format. The first third of the book, while concentrating on the clinical aspects of sickle cell disease and the thalassaemia disorders, also covers other less common haemoglobinopathies, including unstable haemoglobins, methaemoglobinaemia, and haemoglobins of altered oxygen affinity. The middle 35 pages are prefaced by the enigmatic statement that haemoglobin was described by the American physiologist LJ Henderson as the second most interesting

substance in the world. This section goes on to provide a crash course in protein biochemistry, haemoglobin function, red cell metabolism, and molecular biology as applied to haemoglobin. At the end of this section a number of illustrations (a table of amino acid substitutions in common abnormal haemoglobins, and 10 figures) are grouped together. The final 78 pages are devoted to an extensive glossary of clinical, biochemical, and genetic terms used in the field. The sides of the pages of the four main sections are marked to allow their easy identifications.

The title and preface indicate that the book is directed to those 'who care for the disease rather than those who suffer from it'. Its concise style will be heavy going for those without a scientific background, while medical readers should not expect more than very general guidance to the clinical management of patients and the problems presented by this group of disorders. Where drug treatment is mentioned the nomenclature is North American. The primer is at its strongest in the section dealing with laboratory diagnosis, the latter being nicely illustrated in application to a series of eight clinical problems to be found at the end of the first section. The book can be recommended as a remarkably inexpensive guide to the scientific background of the field.

M J PIPPARD

British Paediatric Association

The British Paediatric Surveillance Unit

The British Paediatric Surveillance Unit (BPSU) was set up to provide a method of nationwide disease surveillance particularly orientated to the study of rare childhood disorders, including infectious or infection related conditions of uncertain aetiology or epidemiology. It is a joint venture of the British and Irish Paediatric Associations, the Communicable Disease Surveillance Centre (CDSC) of the Public Health Laboratory Service (PHLS), and the Department of Epidemiology of the Institute of Child Health, London. It was first set up in July 1985 and became fully operational in July 1986. This report summarises the history and operation of the BPSU and presents some results from the activities of its first year.

History

The BPSU developed from the collaboration between the BPA and CDSC to improve the surveillance of infection and associated conditions in children that could not be monitored through existing data collection systems, such as laboratory reporting. This began in 1981 with Reye's Syndrome and was later extended to include haemolytic uraemic syndrome, Kawasaki disease, and haemorrhagic shock encephalopathy syndrome.

Although the voluntary clinical reporting system for these conditions met with enthusiastic support, it was felt that a more active method of case gathering would achieve the higher levels of ascertainment necessary for reliable documentation of trends in rare disorders. Furthermore as the BPA and its members were receiving an increasing number of requests from individual research workers to report a range of rare conditions there was a need to improve the efficiency of research without losing the goodwill of clinicians being asked to report patients under their care.

Objectives

The BPSU has two principal objectives: firstly, to involve paediatricians in the reporting and surveillance of uncommon childhood conditions of importance for public health (particularly those associated with infection), and those rare conditions for which

ascertainment on a national scale is necessary for research. This would include studies, for example, of incidence and prevalence that would generate aetiological hypotheses and provide data for monitoring preventive programmes. Secondly, to provide a unified reporting scheme that is simple, flexible, minimises paperwork, and yet is capable of rapid response to an 'epidemiological emergency'—for example, the detection and monitoring of 'new' diseases of environmental origin, or the surveillance of a rare adverse vaccine reaction.

Organisation and funding

The unit is located in the BPA Office and is staffed by a full time administrator and a part time medical coordinator and clerical officer. It is managed by a Steering and a Scientific Advisory Committee, the three parent bodies being represented on both of these. The BPSU depends almost entirely on charitable and commercial funding for its existence and it now seeks a financial contribution, where possible, from the investigators whose studies it helps.

Methodology

(1) THE MAILING OPERATION

A report card listing the current 'menu' of reportable conditions is sent monthly to all consultant BPA and Irish Paediatric Association members. After having indicated cases of any of these disorders seen in the preceding calendar month or, if none have been seen, having checked a 'nil return' box, the cards are returned to the BPSU. 'Positive' notifications are forwarded to the appropriate research workers who then contact the reporting paediatricians for further information. The mailing operation is sufficiently flexible to allow for surveys to be conducted in one or more regions if this is appropriate to a particular investigator's study design.

(2) INCLUSION OF STUDIES

The Unit's Scientific Advisory Committee meets monthly to consider proposals from investigators. An introductory booklet containing guidelines for

these submissions have been produced. Investigators are encouraged to discuss their plans at an early stage with the medical coordinator and help with study design and constructive criticism of methodology has been an important BPSU activity. In its review procedure the committee considers certain points including: the importance of the research question; the estimated incidence of the condition; the acceptability of the response (usually a questionnaire) to a 'positive' return; the proposed duration of the study and demonstration of adequate resources for its completion. Once accepted a condition can, if necessary, be added to the report card for the next month. A summary protocol for the study that includes case definition, reporting instructions, and the name and address of the investigator(s) is also sent at this stage to all respondents, who have been provided with a special folder to facilitate the storage of protocol cards as studies start and finish. Several paediatricians have commented on the educational usefulness of these protocols, which could heighten diagnostic awareness of rare disorders.

(3) MONITORING THE BPSU

The effectiveness of the Unit can be measured in several ways. First is the subjective or objective opinion of the investigators. The latter might include a comparison with a previous method of case ascertainment or with a concurrent alternative system—for example, death certificates, computerised hospital inpatient data. Second is the monitoring of the proportion of 'positive' reports that are subsequently confirmed (investigators are asked to make returns to the BPSU indicating 'true' cases, duplicate reports, and reporting errors). Third is the response of members in returning cards. Members who consistently fail to return their cards are sent a series of reminder letters seeking reasons for non-response and requesting future cooperation. Finally, the perceived value of the Unit as a research tool could be expected to be reflected in continuing applications for new studies to be included.

(4) BPSU REPORTS

The BPSU has produced two annual reports (available from its office) and also regular quarterly reports in the Communicable Disease Report of the PHLS. This paper is the first of a series to be produced six-monthly in Archives and to which investigators will be asked to contribute observations from their studies. In addition tabulations of regional response rates have been included in mailings periodically in order to introduce a 'competitive' element to participation.

BPSU Activities July 1986 – June 1987

(1) PARTICIPATION IN THE SCHEME

The response rate, among about 800 paediatricians who are sent the month card, rose from 73% in the first month to 89% after one year (this is calculated as the percentage returned within 90 days after each mailing). This rate has remained stable over the last months of the year. There were noticeable regional differences that ranged from 100% in some months (North Scotland, East Anglia, Trent) to a minimum in one month of 68% (West Scotland, December 1986).

Because lack of response may have reflected shortcomings of the scheme (either administrative or due to members' dissatisfaction), persistent non-participants (non-return for three consecutive months) have been contacted to ascertain their reasons. Numbers in three such cohorts declined from 69 to eight and only a handful of these expressed criticism of the BPSU as their reason for non-compliance. It is unlikely that 100% response rate will be consistently achieved given the vagaries of change of address, leave, and retirement. Continuing close attention to non-respondents should, however, minimise the non-response rate and ensure that the mailing list is kept up to date.

(2) CONDITIONS REPORTED

The table indicates the conditions that have been included on the cards during the year, numbers reported, and the numbers that were 'valid'. Those 'not yet known' reflect cases still under investigation by the research workers.

All current investigators have expressed satisfaction with the BPSU, especially those who previously ascertained such cases with a different system. The effect on reporting of Reye's syndrome, Kawasaki disease, and haemolytic uraemic syndrome is shown in the figure—a particularly dramatic increase was seen in Kawasaki disease reports. The initial increase in Reye's syndrome was discouraging as this coincided with the withdrawal of paediatric aspirin preparations. Further analysis showed, however, that many of these initial reports were 'old' cases and duplicates and the continued decline of Reye's syndrome, despite improved ascertainment, has been an important measure of this intervention. The trends shown for haemolytic uraemic syndrome reflect the seasonal distribution of this condition with its late summer–autumn peak.

(3) PROPOSALS FOR NEW STUDIES

The Unit received 11 preliminary proposals for new surveys over the year. Six of these were subsequently submitted formally to the Scientific

Table Conditions included on the reporting cards and number of notifications

Condition	Total reports July 1986– June 1987	No (%) valid		
		Yes*	Not†	Not known‡
AIDS in childhood¶	37	18 (49)	13 (35)	6 (16)
Neonatal herpes¶	21	8 (38)	9 (43)	4 (19)
Reyes syndrome	49	20 (41)	19 (39)	10 (20)
Kawasaki disease	120	96 (80)	10 (8)	14 (12)
Haemolytic uraemic syndrome	51	35 (69)	1 (2)	15 (29)
Haemorrhagic shock encephalopathy syndrome	17	12 (71)	2 (12)	3 (18)
Subacute sclerosing panencephalitis¶	33	25 (76)	4 (12)	4 (12)
X-linked anlytic ectodermal dysplasia§	13	2 (15)	0	11 (85)
Insulin-dependent diabetes¶	20	20 (100)	0	0
Lowe syndrome	15	5 (33)	1 (7)	9 (60)
Total	376	241 (64)	59 (15.7)	76 (20)

* Meets case criteria

† Reporting error, duplicate, revised diagnosis

‡ Still being followed up (30 September 1987)

§ Three month surveys

¶ South Western Region only

¶ Figures include cases ever seen (AIDS), or seen past year (others) as well as new cases in past month

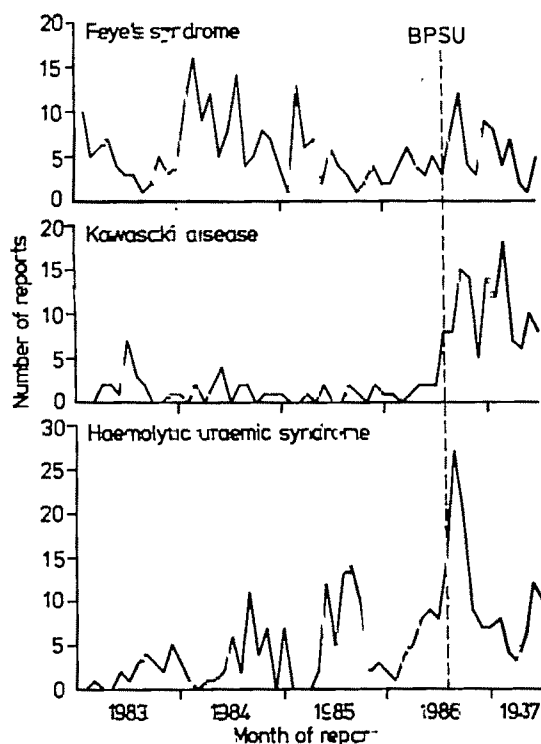


Figure The effect of the BPSU system on reporting

were accepted and will be added to the 'menu' in due course, others are still under consideration.

Comment

The BPSU is a unique approach to the surveillance of the less common communicable and infection related diseases in children and to the study of rare paediatric disorders. Its first year has gone remarkably well for such a new venture, judging from response rates, satisfaction of investigators, and the many important new research proposals. Its current and future success depends very largely on the continued support of British paediatricians who give their time to helping national studies that, by their nature, are usually unable to acknowledge individual contributions. It will therefore be important to retain this goodwill by limiting the number of reportable conditions on the card at any one time; by ensuring that the studies included are important, interesting, and of limited duration so that the conditions change periodically, and by providing feedback. This should in turn increase both professional and public knowledge of rare paediatric disorders that, taken together, account for a considerable proportion of childhood morbidity and mortality in the British Isles.

Advisory Committee. Conditions to be studied included a range of rare metabolic, haematological, neoplastic, and infectious disorders and one other proposal was for a survey of near drowning. Some

S M HALL
(BPSU Medical Coordinator),
and M GLICKMAN
(BPSU Administrator)

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Contra-Indications

Ribavirin is contra-indicated in females who are or may become pregnant and it should be noted that ribavirin can be detected in human blood even four weeks after oral administration has ceased.

Precautions

In infants requiring assisted ventilation, Virazid should only be used when there is constant monitoring of both patients and equipment.

Side Effects

Several serious adverse events occurred in severely ill infants with life threatening underlying disease many of whom required

assisted ventilation. These events included worsening of respiratory status, bacterial pneumonia and pneumothorax. The role of ribavirin aerosol in these events has not been determined.

Anaemia has been reported with oral and intravenous administration but no such incidents have been reported with aerosol administration. Reticulocytosis has been reported with aerosol use.

Warnings

Precipitation of the drug in respiratory equipment and consequent accumulation of fluid in the tubing has caused difficulties for patients requiring assisted ventilation.

In infants requiring assisted ventilation Virazid should only be used when there is constant monitoring of both patients and equipment.

Directions for use during assisted ventilation are given in the SPAG manual which should be read carefully before such administration.

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EDITED BY MICHAEL W ADLER

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